UNIVERSITÀ
DEGLI STUDI
DI PADOVA

Università degli Studi di Padova

Department of Cardiac, Thoracic and Vascular Sciences

PH.D. COURSE IN: SCIENZE MEDICHE, CLINICHE E SPERIMENTALI

CURRICULUM: SCIENZE CARDIOVASCOLARI

CICLO XXIX

Primary Cardiac Tumors in the Veneto Region of Italy: epidemiology and surgical pathology study in a 12-years interval

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SUMMARY

Background: Primary cardiac tumors represent a rare entity in cardiac surgery but have the potential to cause significant morbidity if not treated in an appropriate and timely manner. The aim of the study was to investigate the incidence, histopathology and survival characteristics of patients who underwent surgical resection in Veneto Region in the time interval 2005-2016.

Material and Methods:

A Regional Registry of primary cardiac tumors was created from data of 6 Cardiac Surgery Institutions of Veneto Region (Mestre, Treviso, Mirano, Padova, Vicenza and Verona), gathering retrospectively all consecutive patients who underwent surgical resection in time interval 2005-2016 (12 years). Data included histopathology reports. The tumors have been classifield and incidence estimated. A subgroup of this cohort (Mestre, Mirano, Treviso) was evaluated in term of clinical outcomes, follow-up and surgical success, defined as disease-free survival.

Results:

The study population included 279 patients, average age of 59.8±16.8 years (<1 year to 83 years), female gender in 55.6% (155 women). The incidence of primary cardiac tumors in Veneto Region was constant every years (0.47%) and the distribution per age showing a peak of incidence in people 60–70 years of age (n=75, 26.88%). 254 patients (91%) were affected by benign primary cardiac tumors and 25 (9%) patients by malignant cardiac tumors. Among the benign cardiac tumours group, the majority (70.08%) were myxomas, followed by papillary fibroelastomas (18.90%), lipomas (3.15%), hemangioma (2.76%), rhabdomyomas (0.79%), leiomyoma (0.79%) and fibroma (0.39%). In the malignant group the most prevalent histotype was angiosarcoma (n=8, 32%), followed by lymphoma (n=6, 24%), leiomyosarcoma (n=3, 12%) and undifferentiated sarcoma (n=6, 24%). Cardiac myxoma is the most frequent primary cardiac tumor in our surgical

series and his location was mostly in the left atrium (n=162, 91%), followed by the right atrium (n=16, 9%).

The location of the second most frequent primary cardiac tumor (papillary fibroelastoma) was the valvular endocardium in 41 patients: aortic valve (n=23, 47.9%), mitral valve (n=13, 27.1%), tricuspid valve (n=6, 12.5%), and pulmonary valve (n=1, 2.1); and the mural endocardium in 7 patients (left ventricular cavity and right atrial cavity).

Subgroup of general population was analyzed by processing clinical, surgical and follow-up data. Seventy-nine consecutive patients, 41 female (51.9%) and 38 male (48.1%), were referred for surgical resection of a cardiac mass at three Cardiac Surgery Institutions of the Veneto Region (Mestre, Treviso, Mirano). The median age was 63.3±15.2 years. All tumors were detected by transthoracic and transesophageal echocardiography. The incidence of benign neoplasms was much higher than malignant masses; of the benign tumors, 77.2% (n=61 patients) were myxomas. Of the malignant tumors, synovial sarcoma was the most common cardiac tumor (n=2 patients, 2.5%). The clinical pre-operative presentation was: dyspnea with NYHA Class II-III in 36.7% patients, chest pain in 29.1% and embolic complications in 8.8% of which 6.7% cerebral ischemic events. The location of the tumors was: 54.7% in the left atrium, 8.9% in the right atrium, 5.1% in the ventricles, 10.1% on the valves. Eleven patients underwent a mini-invasive surgical approach. Early (30 day) mortality was 1.2% (n=1), due to septic shock and multiorgan failure. Late mortality was 10.1% (n=8). One malignant tumor (angiosarcoma) and one benign tumor (myxoma) recurred during follow-up requiring re-intervention.

Conclusions:

Epidemiological data of primary cardiac tumours are still based on post-mortem studies. The incidence and prevalence of cardiac neoplasms, in general, have shown little change over time. Surgical pathology started with the advent of cardiac imaging and open heart surgery when cardiac

neoplasms were diagnosed during life. The purpose of Veneto Registry is to discuss the actual prevalence and pathology of primary cardiac tumours.

Histology with immunohistochemistry of any cardiac mass is mandatory for diagnosis, therapy and prognosis. The surgical results suggest that complete surgical resection of primary benign cardiac tumors is associated with very-good long-term survival and recurrence is rare. Immediate surgical treatment was indicated because of the high risk of embolization or of sudden cardiac death.

PART I

GENERAL SURVEY of CARDIAC TUMORS

CHAPTER 1

INTRODUCTION

Although the term tumour generally recalls the idea of "cancer", at a cardiac level most primary tumours are biologically benign and malignancy is haemodynamic, due to obstruction of the blood flow because of intra-cavitary growth and embolism following neoplastic fragility with ischemic damage of distal organs (1-3).

The first description of cardiac tumors was made by Matteo Realdo Colombo in 1559 in his book *De Re Anatomica* (1, 4-6). While performing the autopsy of Cardinal Gambaro from Brescia, while he was archiater in Rome at that time, Colombo discovered a left ventricular mass described as follows in Latin "*In Cardinali Gambara Brixiano tumorem praedurum*, *et ad ovi magnitudinem in sinistro cordis ventricolo Romae vidi*, *ubi illum in affinium gratiam dissecarem*" ("*in Rome I saw a solid tumour*, *large like an egg*, *in the left ventricle of Cardinal Gambaro of whom I was committed by the Pope to make autopsy*"). Most likely it was a post-infarction endocavitary apical thrombus rather than a true neoplasm.

An atrial tumor that was thought to cause valvular obstruction was described in 1809 by Burns (7). The first series of cardiac tumors that matched what we now recognize as myxoma was reported in 1845 by King (8).

In 1931, Yates published 9 cases of primary cardiac tumors and established a classification system (9). All of these tumors were postmortem reports, with the first antemortem diagnosis reported in 1934 by Barnes et al of a cardiac sarcoma with abnormal electrocardiogram and a metastatic lymph node that allowed tissue diagnosis (10). Surgical intervention with excision of a cardiac tumor was first reported with success, by Beck in 1942, involved removal of a teratoma external to the right ventricle (11).

The first book on cardiac tumours was published in 1945 by Ivan Mahaim, from the University of Lausanne with the title *Les tumeurs et les polypes du coeur*: *etude anatomo-clinique* (3) *(Figure 1.1).*

Figure 1.1 *A) Title page of the book by Ivan Mahaim on cardiac tumors, published in 1945. B) Drawing of a left atrial myxoma in the book by Mahaim, described as a "pedunculated polyp" accounting for functional mitral stenosis. Mahaim I, Les Tumeurs et les Polypes du Coeur: Etude Anatomoclinique, 1945.*

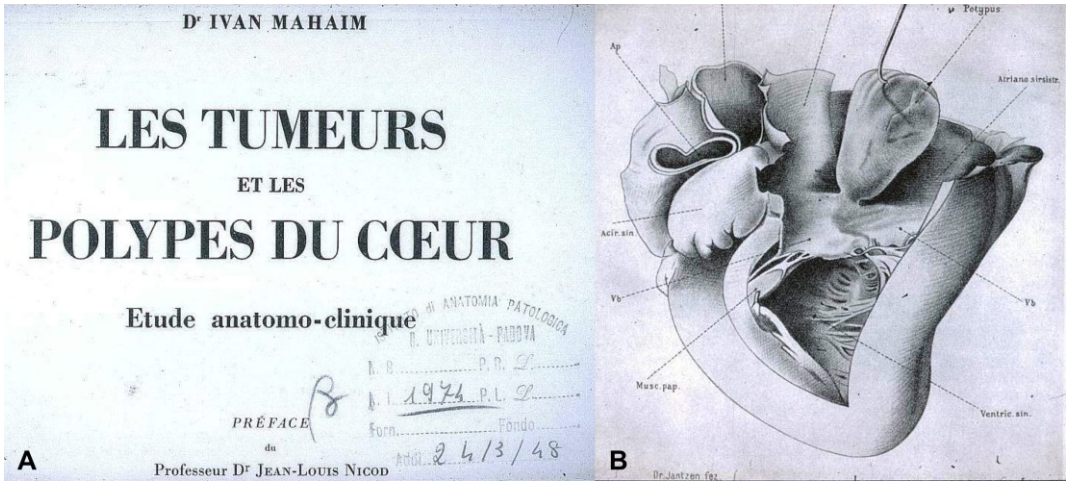

Figure 1.2 *Ivan Mahaim*

At the Institute of Pathological Anatomy of the peaceful Lausanne, the young cardiac pathologist Mahaim (*Figure 1.2*) wrote an extraordinary book, that was a collection of personal observations at postmortem as well as of literature review, and represented a milestone publication on the topic of cardiac tumors for several generations of pathologists and physicians involved in the field. From him we learned that cardiac myxoma (called in French "*le polype*" due to its resemblance to a pedunculated gastro-enteric polyp), can have a clinical presentation with syncope or dyspnea due to

atrio-ventricular valve orifice occlusion (functional mitral stenosis), with peripheral artery occlusion due to embolic phenomena, or can be totally asymptomatic being an incidental finding ("*les polypes silencieux*"). Although these were all autopsy cases, Mahaim was optimist on the perspectives of Medicine. While treating atrial myxoma ("*Le polype du coeur*"), the most frequent cardiac tumor (nearly two-thirds of primary heart neoplasms), he said "*...surgical resection of atrial polyp encounters apparently unsurmountable difficulties*. *However*, *we should not give up because of this feeling*. *In any field of science*, *with technological progress*, *the impossible is just a moment during the evolution of our powers*. *As Mummery said about alpinism*, *the inaccessible peak becomes an easy route for ladies...*" (1,3). In fact, some years later the era of "surgical pathology" started with the advent of cardiac imaging and open heart surgery in the '60s, when cardiac neoplasms were diagnosed during life and not only in the autopsy room and became surgically resectable with excellent long-term survival (12,13).

On the contrary, in 1951 Prichard (12) manifested a pessimistic attitude by saying "*...of the surgical treatment of these tumours we never heard…*" (3). Surprisingly, in the same year 1951, Goldberg et al. (13) for the first time successfully made a clinical diagnosis of left atrial myxoma using angiography (14), and Maurer in 1952 reported the successful removal of a left ventricular lipoma (15). This paucity of surgical success changed because of 2 events: 1) the introduction of cardiopulmonary bypass (CPB) in 1953 by John Gibbon (16), allowing a safe and reproducible entry into the cardiac chambers, and 2) the introduction of echocardiography, allowing easy, noninvasive imaging of intracardiac structures and masses. Bhanson made an early attempt at removing an intracardiac right atrial myxoma in 1952 by using caval inflow occlusion, but the patient expired 24 days later (17). The first successful removal of an intracardiac tumor is generally credited to Crafoord from Sweden, who in 1954 removed a left atrial myxoma using CPB (18). Progress from this point was rapid; by 1960, 60 successful cases of atrial myxoma removal had been reported, with increasing use of angiography for detection and CPB for removal (19). Today,

operation for benign cardiac tumors, although still uncommon, is generally carried out with low morbidity and mortality.

However, the historical watershed in the diagnosis and treatment came in the 1980s, with the advent of non-invasive imaging, i.e., echocardiography which, together with computed tomography (CT) and cardiac magnetic resonance (CMR), substantially improved diagnosis and subsequent treatment. It is possible to easily visualize cardiac tumors at the first onset of symptoms or even incidentally, during routine echo diagnostic procedures, and send the patient promptly to the surgeon for resection with a nearly 100% success in the benign forms. Before the 1980s cardiac tumors were a postmortem finding, thereafter they became almost exclusively a clinical and surgical observation (20).

The role of the pathologists is now to establish in vivo the nature of the resected mass (non-neoplastic, benign, or malignant neoplasms) and to make the differential diagnosis with secondary neoplasms. The advent of immunohistochemistry to characterize the antigenic markers, by using monoclonal and polyclonal antibodies, leads to major advances in the diagnosis of primary and secondary cardiac tumors as in other fields of oncology, but particularly of malignant primary tumors, where the tumor cell of origin can be the endothelial cell, fibroblast, cardiomyocyte, smooth muscle cell, adipocyte. (1,21).

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CHAPTER 2

EPIDEMIOLOGY AND INCIDENCE

The cardiac tumor is rarely encountered, and its incidence is very low compared to tumors of other organs. In the past, cardiac tumors were very difficult to diagnose before life and were often discovered incidentally at autopsy. Recent advances in diagnostic techniques such as echocardiography and CT enabled clinical diagnosis during lifetime, and pathological diagnosis of tumor can be obtained by surgically removed tumors or surgical/endomyocardial biopsy. By cumulate pathological and clinical data, it became evident that many varieties of tumors occur in the heart and great vessels as in other organs.

2.1 The incidence of cardiac tumors at autopsy

Epidemiological data of cardiac tumors are still based on postmortem studies (1,2).

The referred prevalence is very low, ranging from 0.0017% to 0.33% in autopsy series, the variability being strongly influenced by when and where the data have been collected and according to diagnostic methods (1-6) *(Table 2.1)*.

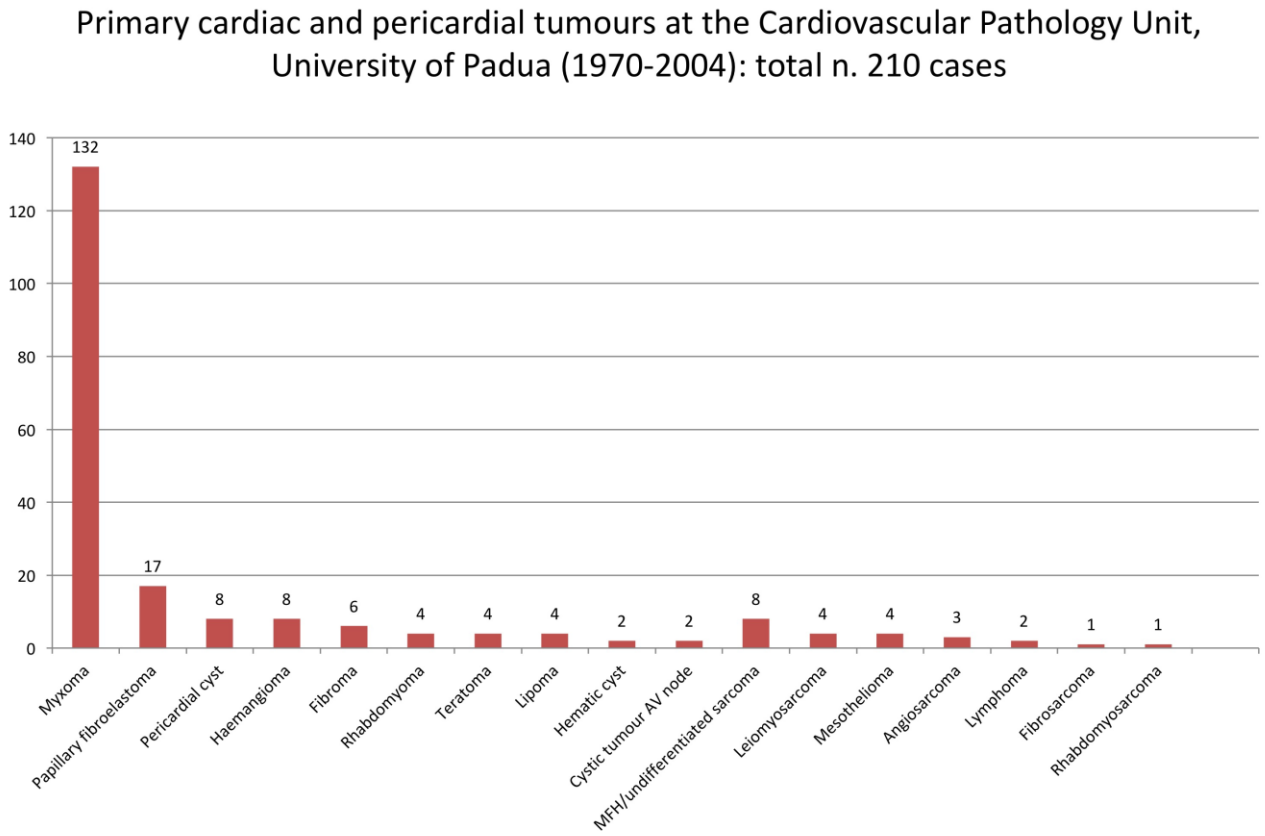
Pollia and Gogol (7) reported the highest incidence of primary cardiac tumors as 0.33 % (154 cases) in 46,072 autopsy cases, while Straus and Merliss (9) reported the lowest incidence as 0.0017 % (8 cases) in 480,000 autopsy cases. Reynen (10) reported the incidence as 0.021% in 731,309 autopsy cases by summarizing the autopsy data from literature. Reports on cardiac tumors in children are scarce, with a reported incidence at autopsy of 0.01% by Nadas and Ellison (12).

At the Institute of Pathology of the University of Padua in the time interval of 1967–1976, on 7,460 autopsies the prevalence of primary cardiac tumour was 1 out of 2,000 and that of secondary tumours was 1 out of 100 autopsies, with a secondary/primary ratio of 20:1 (*Figure 2.1*)(1,13, 14).

Table 2.1 *Incidence of primary cardiac tumors diagnosed at autopsy. Modified from Wold LE, Lie JT. Cardiac myxomas: a clinipathologic profile. AM JPathol. 1980:101;219-40.*

Authors	**Autopsy cases**	**Primary cardiac tumors**	**Incidence(%)**
Pollia [7]	46,072	154	0,33
Benjamin[8]	40,000	12	0,003
Straus [9]	480,000	8	0,0017
Reynen[10]	731,309	15,357	0,021
Mayo clinic			
Lymburner[11]:1912-1931	8,550	4	0,047
Wold[3]: 1954-1973	23,673	41	0,17

Figure 2.1 *Primary cardiac and pericardial tumours at the Cardiovascular Pathology Unit, University of Padua (1970-2004): total n. 210 cases.*



2.2 Human cardiac tumors

Cardiac and pericardiac masses include benign and malignant, both primary and secondary tumors, and nontumoral lesions. Concerning the epidemiology and prevalence of various histotypes, in the Armed Forces Instiute Pathology (AFIP) data (15), cardiac myxoma is the most common cardiac tumor accounting for 24–37% of them, following by papillary fibroelastoma (8.0%). According to the histological classification by the World Health Organization (5), among the benign cardiac tumors, the majority (63%) are myxomas, followed by papillary fibroelastomas (8%). Angiosarcoma, unclassified sarcoma, and malignant fibrous histiocytoma represent the main malignant primary cardiac tumors. In comparison with adults, the incidence of cardiac tumors in children is very low (12,15). With rate of rhabdomyoma and fibroma and histiocytoid cardiomyopathy also is relatively high, but cardiac myxoma is the most common histotype even in children (1,15,16). In children, malignant tumors originating from the heart are very rare, and leiomyosarcoma, unclassified sarcoma, and rhabdomyosarcoma (10,15).

The age at diagnosis of cardiac tumors is different for each tumor subtype. According to the AFIP data (15), rhabdomyoma and teratoma occur in infancy, rhabdomyosarcoma and cardiac fibroma are common in the adolescence, myxoma, papillary fibroelastoma, mesothelioma and lipoma tend to occur in the elderly (1, 15,17). The data reported by the AFIP (15) are questionable, since AFIP achieve a precise diagnosis as a tertiary international center for consultancy of difficult cases.

2.3 Secondary (metastatic) cardiac tumors

Metastatic cardiac tumors are more frequent than primary cardiac malignant tumors (1,2,18-20), with a ratio of cardiac metastases to primary malignant tumors 100:1 to 1,000:1 (15). The rates of cardiac metastasis reported in the literature are highly variable (*Table 2.2*).

Table 2.2 *Reported incidences of metastatic cardiac tumors in the literature. Modified from Basso et al., Cardiac Tumor Pathology, 2013.*

Author	**Neoplasms N.**	**Cardiac Metastases N. (%)**
Walther [21]	2,027	46 (2,3)
Wills [22]	342	17 (4,9)
Hanfling [23]	694	127 (18,3)
Berge &Sievers [24]	2,595	122 (4,7)
Kline [25]	716	61 (8,5)
Karwinski & Svendsen [26]	2,564	130 (5,1)
Mukai et al. [27]	6,240	953 (15,0)
Manojlovic [28]	477	39 (8,2)
MacGee [29]	1,311	57 (4,3)
Silvestri et al. [30]	1,928	162 (8,4)
Bussani et al. [20]	7,289	662 (9,1)

Mukai et al. (27) reported that during a 10-year period (1976–1985), only one case of a primary pericardial malignant mesothelioma (0.038%) was identified among 2,649 autopsies of malignant tumors at the National Cancer Center Hospital, in contrast, there were 407 cases (15.4%) in which heart and/or pericardium were secondarily involved with a malignant tumor from other organs. Butany et al. (31) reported two primary malignant tumors originated from the heart (0.017%) and 264 metastatic (2.31%) among 11,432 autopsies (with a ratio of primary malignant to metastatic tumors 1:132). Bussani et al. (19) reported 662 cases among 7,289 autopsy cases with malignancies (9.1%), with a decreasing occurrence with age (16.8% in people <64 vs 8.5% in people >85), probably due to less biological aggressiveness in the elderly.

In a consecutive surgical pathology series of 210 primary cardiac neoplasms studied at the

University of Padua, 89% were benign and 11% malignant. The collected data in Padua are much more reliable since they are a consecutive surgical series covering 35 years span (32) (*Figure 2.1*). Any extracardiac malignant tumour may metastasise to the heart, however, melanoma, lung and breast carcinoma show the highest cardiotropism, reflecting also the most common incidence of these cancers. The sites of the metastatic tumor in the heart are the myocardium, the pericardium, and both myocardium and pericardium. Mukai et al. (27) reported that among 407 cases of cardiac metastasis, metastasis to the myocardium were 169 cases (41.5%), followed by epicardium 136 cases (33.4 %), pericardium 78 cases (19.2%), and endocardium 24 cases (5.9%). Butany et al. (31) reported that among 193 cases of cardiac metastasis, metastasis to the pericardium were 127 cases (65.8%), myocardium 56 cases (29.0%), epicardium 48 cases (24.9%), and endocardium 6 cases (3.1%) (*Table 2.3*). Formerly, most of the metastatic cardiac tumors have been so far reported in autopsy cases. Recent advances of diagnostic imaging methods by CT, CMR, and echocardiography enabled to discover metastasis to the heart early even in the absence of symptoms related to the heart, such as arrhythmia and heart failure (33).

Table 2.3 *Metastatic sites of the heart and the pericardium. Modified from Amano J. et al. Textbook of cardiac tumors, 2011.*

Sites	**Mukai**[27]	**Butany** [31]
Heart/pericardium	407	264
Heart: with or without pericardial involvement	329	137
Pericardium only	78	127
Extent of involvement		
Pericardium	78 (19,2%)	127 (65,85)
Epicardium	136 (33,4%)	48 (24,9%)
Myocardium	169 (41,5%)	56 (29,0%)
Endocardium	4 (5,9%)	6 (3,1%)

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CHAPTER 3

CLASSIFICATION OF TUMORS OF THE HEART AND GREAT VESSELS

Among tumors of the heart and great vessels, about 90% of the surgically excised tumors are benign (1-3). Since there is lack of histogenetical and pathological evidence of true neoplastic nature for papillary fibroelastoma, histiocytoid cardiomyopathy, lipomatous hypertrophy of the interatrial septum or cystic tumor of atrioventricular node, pathological classification is very difficult for these tumors (4). Moreover, because origin and cell differentiation of many cardiac tumors is not yet determined, it is very difficult to classify over on thid thesis. According to the well-known classification of ‘‘Tumors of the heart and great vessels’’ (Armed Forces Institute of Pathology: AFIP) published in 1996 (5) (*Table 3.1*), cardiac tumors, including both cardiac tumors and pericardial tumors, are classified into benign and malignant. Sarcomas of the aorta and pulmonary artery, sarcomas of the inferior vena cava, and leiomyomatosis of veins are classified in different categories. Benign cardiac tumors are further classified as tumors of unknown histogenesis, tumors of cardiac muscle, tumor of fibrous tissue, vascular tumors and tumor-like lesions, tumors and proliferations of fat, tumors and tumor-like lesions of mesothelial cells, tumors of neural tissue, tumors of smooth muscle, and tumors of ectopic tissue. Malignant cardiac tumors are classified as sarcomas, malignant germ cell tumors, hematologic tumors, mesothelial malignancies, and metastatic tumors to the heart.

Table 3.1 *Classification of ''Tumors of the heart and great vessels'' (Armed Forces Institute of Pathology: AFIP). From Burke A, et al.,Tumors of the heart and great vessels. Atlas of tumor pathology, 1996.*

- Benign cardiac tumors
  - Tumors of unknown histogenesis
    - Myxoma
    - Papillary fibroelastoma
  - Tumors of cardiac muscle
    - Rhabdomyoma
    - Histiocytoid cardiomyopathy (purkinje cell hamartoma)
    - Miscellaneous hamartomas
  - Tumors of fibrous tissue
    - Fibroma
    - Solitary fibrous tumor of pericardium
    - Benign fibrous histiocytoma
    - Inflammatory pseudotumor
  - Vascular tumors and tumor-like lesions
    - Varix
    - Hemangioma
    - Hemangioendothelioma
    - Hemangiopericytoma
    - Lymphangioma
  - Tumors and proliferations of fat
    - Lipomatous hypertrophy, interatrial septum
    - Lipomatous hamartomas of cardiac valves
    - Lipoma
    - The fatty heart
  - Tumors and tumor-like lesions of mesothelial cells
    - Mesothelial cysts
    - Mesothelial/monocytic incidental cardiac excrescences
    - Mesothelial papilloma
  - Tumors of neural tissue
    - Granular cell tumor
    - Schwannoma/neurofibroma
    - Paraganglioma
  - Tumors of smooth muscle
    - Leiomyoma
    - Intravascular leiomyomatosis
  - Heterotopias and tumors of ectopic tissue
    - Bronchogenic/foregut cysts
    - Tumors of the atrioventricular nodal region
    - Teratoma
    - Ectopic thyroid
    - Intrapericardial thymoma
- Malignant cardiac tumors
  - Sarcomas
    - Angiosarcoma
    - Malignant fibrous histiocytoma
    - Unclassified sarcoma
    - Myxosarcoma
    - Fibrosarcoma
    - Leiomyosarcoma
    - Rhabdomyosarcoma
    - Osteosarcoma
    - Synovial sarcoma
    - Malignant schwannoma (malignant peripheral nerve sheath tumor)
    - Malignant mesenchymoma
    - Malignant hemangiopericytoma
    - Kaposi's sarcoma
  - Malignant germ cell tumors
  - Hematologic tumors
    - Lymphoma
  - Granulocytic sarcoma
  - Mesothelial malignancies
    - Malignant mesothelioma
  - Metastatic tumors to the heart
- Sarcomas of the aorta and pulmonary artery
  - Luminal (intimal) sarcoma
    - Unclassified sarcomas
    - Malignant fibrous histiocytoma
    - Angiosarcoma
    - Osteosarcoma
    - Chondrosarcoma
    - Leiomyosarcoma
    - Malignant mesenchymoma
  - Mural sarcomas
    - Leiomyosarcoma
    - Angiosarcoma
    - Malignant fibrous histiocytoma (MFH)
    - Unclassified sarcomas
- Sarcomas of the inferior vena cava
  - Mural leiomyosarcoma
  - Luminal (intimal) sarcoma
- Leiomyomas of veins

In the 2004 WHO classification, tumor of the heart are divided into three categories: benign tumors and tumor-like lesions, malignant tumors, and pericardial tumors (6) (*Table 3.2*).

Table. 3.2 *2004 WHO classification of tumors of the heart. From Burke AP, et al., Tumors of the heart. In: Travis WD, et al., JARC Press; 2004.*

Benign tumors and tumor-like lesions
Tumors of muscle cell differentiation
1. Rhabdomyoma
2. Histiocytoid cardiomyopathy/purkinje cell hamartoma
3. Hamartoma of mature cardiac myocytes
4. Adult cellular rhabdomyoma
Pluripotent mesenchymal tumor
1. Cardiac myxoma
2. Papillary fibroelastoma
Haemangioma
Tumors myofibroblastic cell differentiation
1. Cardiac fibroma
2. Inflammatory myofibroblastic tumor/Inflammatory pseudotumor
Cardiac lipoma
Cystic tumor of atrioventricular node
Malignant tumors
Cardiac sarcomas
1. Angiosarcoma
2. Epithelioid hemangioendothelioma
3. Malignant pleomorphic fibrous histiocytoma (MFH)/ undifferentiated pleomorphic sarcoma
4. Fibrosarcoma and Myxoid fibrosarcoma
5. Rhabdomyosarcoma
6. Leiomyosarcoma
7. Synovial sarcoma
8. Liposarcoma
Cardiac lymphoma
Metastatic tumors to the heart
Pericardial tumors
1. Solitary fibrous tumor
2. Malignant mesothelioma
3. Germ cell tumors
4. Metastatic pericardial tumors

Benign tumors were classified as tumor showing differentiation into muscle cells, such as rhabdomyoma, adult cellular rhabdomyoma, hamartoma of mature cardiac myocytes, and histiocytoid cardiomyopathy. Cardiac myxoma and papillary fibroelastoma are classified as pluripotent mesenchymal tumors, and cardiac fibroma and inflammatory myofibroblastic tumor as tumor showing differentiation into myofibroblastic cell. This classification does not include benign cardiac tumors with low incidence such as tumors of neural cell or smooth muscle cell differentiation. Most prominent differences of 2004 WHO classification from AFIP classification are malignant tumors. First, epithelioid hemangioendothelioma, formerly considered a benign tumor, has been classified as malignant tumor; undifferentiated sarcoma, previously classified as tumor of unknown origin, is part of malignant pleomorphic fibrous histiocytoma (MFH)/ undifferentiated pleomorphic sarcoma subtype. Moreover, in the 2004 WHO classification, malignant mesenchymoma, osteosarcoma, chondrosarcoma, and many other sarcomas, are considered as independent sarcoma, and myxosarcoma as a subtype of myxoid fibrosarcoma.

Recently, a new WHO classification has been published, taking into account the recent findings on cell differentiations and molecular basis of cardiac tumors (7) (*Table 3.3*).

Tumors are classified as benign tumors, tumors of uncertain biologic behavior, germ cell tumors, malignant tumors and tumors of the pericardium (8). The major changes in tumors of the heart have been: the removal of the term ‘malignant fibrous histiocytoma’ as synonymous with undifferentiated pleomorphic sarcoma; incorporation of epithelioid hemangioendothelioma as an angiosarcoma with low-grade malignance; remarkable expansion of the cytogenetic and molecular genetic characterization of many cardiac tumors; re-introduction of the primary cardiac osteosarcoma and myxofibrosarcoma subtypes. The clinical-pathological entity referred to as intimal sarcomas has been not included in the new WHO classification (9). Intimal sarcoma has been recently reported in the heart as the most frequent sarcoma histotype (10). As in large vessels,

this type of sarcoma is characterized by overexpression of MDM2 as well as alterations in genes like PDGFRA and EGFR that could be targets for novel therapeutic approaches.

Table 3.3 *2004 WHO classification of tumors of the heart. From Travis WD, et al., WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart, 2015.*

Benign Tumors and Tumor-Like Conditions	ICD-O Codes
Rhabdomyoma	8900/0
Histiocytoid cardiomyopathy	
Hamartoma of mature cardiac myocytes	
Adult cellular rhabdomyoma	8904/0
Cardiac myxoma	8840/0
Papillary fibroelastoma	
Hemangioma, NOS	9120/0
Capillary hemangioma	9131/0
Cavernous hemangioma	9121/0
Arteriovenous malformation	9123/0
Intramuscular hemangioma	9132/0
Cardiac Fibroma	8810/0
Lipoma	8850/0
Cystic tumor of the atrioventricular node	8454/0
Granular cell tumor	9580/0
Schwannoma	9560/0
Tumors of uncertain biologic behavior	
Inflammatory myofibroblastic tumor	8825/1
Paraganglioma	8680/1
Germ cell tumors	
Teratoma, mature	9080/0
Teratoma, immature	9080/3
Yolk sac tumor	9071/3
Malignant tumors	
Angiosarcoma	9120/3
Undifferentiated pleomorphic sarcoma	8830/3
Osteosarcoma	9180/3
Myxofibrosarcoma	8811/3
Leiomyosarcoma	8890/3
Rhabdomyosarcoma	8900/3
Synovial sarcoma	9040/3
Miscellaneous sarcomas	
Cardiac lymphomas	
Metastatic tumors	
Tumors of the pericardium	
Solitary fibrous tumor	8815/1
Malignant	8815/3
Angiosarcoma	9120/3
Synovial sarcoma	9040/3
Malignant mesothelioma	9050/3
Germ cell tumors	
Teratoma, mature	9080/0
Teratoma, immature	9080/3
Yolk sac tumor	9071/3

ICD-O, International Classification of Diseases for Oncology; NOS, not otherwise specified.

Table 3.4 *Clinicopathologic Features of primary Heart Tumors. From Travis WD, et al., WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart, 2015.*

	Age			Site in Heart			
Histologic Type	Fetuses, Iinfants	Children	Adults	Layer	Location	Multiplicity	Syndromic Association
Benign congenital tumors							
Rhabdomyoma	++	+		**Myocardium**[a]	Ventricles	Usual	Tuberous sclerosis
Fibroma	+	++	+	**Myocardium**	Ventricle, ventricular septum	Rare	Gorlin syndrome
Histiocytoid cardiomyopathy	++	+/1		Endocardium, myocardium	Ventricles, atrial, AV SA nodes	Always	
Benign acquired tumors							
Myxoma		+/-	++	**Endocardium**	LA, atrial septum RA, atrial septum	Rare	Carney complex
Papillary fibroelastoma			++	**Endocardium**	Valves > atria > ventricles	Occasional	
Hemangioma[b]	+	+	+	Myocardium Endocardium[c]	Atria > ventricles	Unusual	
Lipomatous hypertrophy			++	**Myocardium of atrial septum**			
Lipoma			++	Myocardium, epicardium, endocardium	All sites	Rare	
Inflammatory myofibroblastic tumor[d]	++	+	+/-	**Endocardium**	Valves > atria	Occasional	
Germ cell tumors							
Teratoma	++	+	+/-	Pericardial cavity Ventricular septum (rare)		No	
Yolk sac tumor	++	+		Pericardial cavity Ventricular septum (rare)		No	
Malignant tumors							
Angiosarcoma		+/-	++	All layers	Right atrium, pericardium	Occasional	
UPS/ myxofibrosarcoma	+/-	+/-	++	Endocardium	Left atrium Other sites	Rare	
Rhabdomyosarcoma	+/-	++	+	Myocardium	Ventricles	No	
Leiomyosarcoma		+/-	++	Endocardium	Left atrium	No	
Lymphoma		+/-	++	Myocardium	Right atrium, others	Occasional	

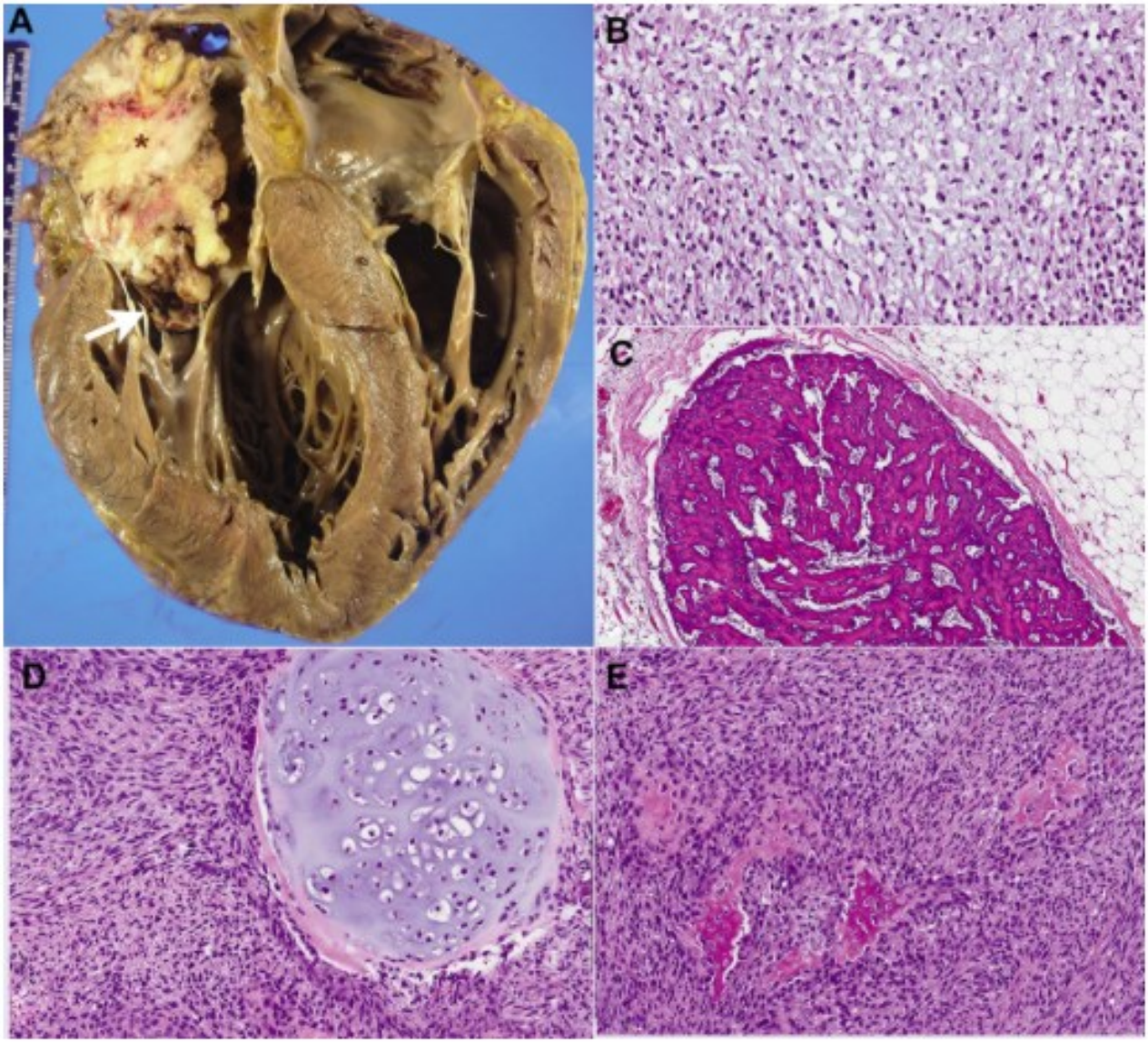
[a]Boldface indicates an exclusive site.

[b]Hemangioma is considered alternatively as a congenital tumor, especially in children.

[c]Especially the capillary type.

[d]Inflammatory myofibroblastic tumors are sometimes considered low-grade malignancies, although none in the heart has metastasized.WHO, World Health Organization; AV, atrioventricular; SA, sinoatrial; LA, left atrium; RA, right atrium; UPS, undifferentiated pleomorphic sarcoma.

Figure 3.1 *Osteosarcoma, left atrium. (A) Autopsy specimen (cut open, four-chamber view) shows an infiltrative, pale and gritty mass (asterisk) centered in the left atrium with contiguous mitral valve invasion (arrow). (B) Some areas were myxoid and relatively bland, similar to myxofibrosarcoma. (C) The bone formation in this invasive area of tumor (into the pulmonary vein) showed well-differentiated osteoid. (D) In some areas, there is chondrosarcoma. (E) Other areas show poorly differentiated osteosarcoma. From Burke A, Journal of Thorac Onc, 2015.*



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CHAPTER 4

CLINICAL MANIFESTATIONS OF CARDIAC TUMORS

The clinical manifestations of cardiac tumors are protean (1). They produce symptoms by their mass effect, local invasion, embolization, or sytemic constitutional manifestations and must be in the differential diagnosis of any patient who presents with one or a combination of the following symptoms (2).

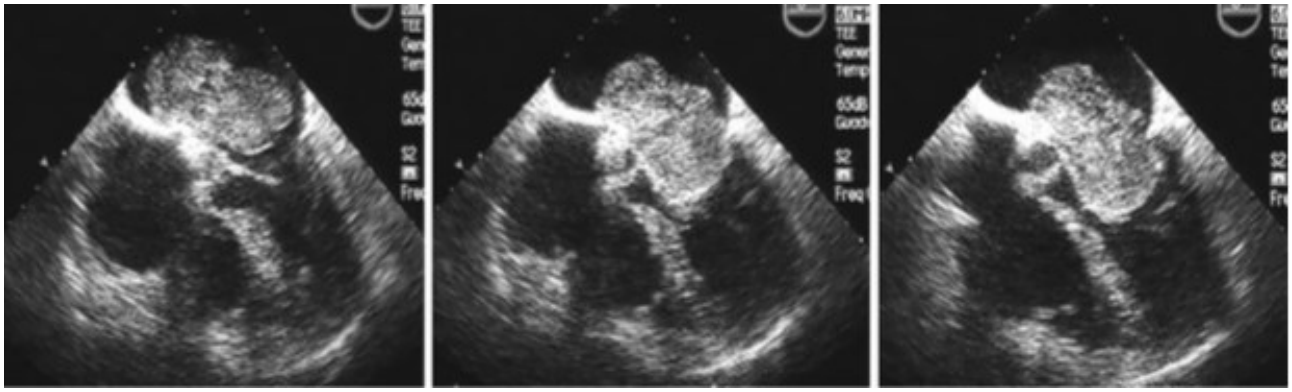
Pericardial Involvement

Neoplastic infiltration of the pericardium can produce pericarditis with resultant haemorragic effusion and tamponade. In addition, pericardium can become non-compliant resulting in a clinical presentation indistinguishable from constrictive pericarditis of infectious or idiopathic origin.

Congestive Heart Failure

The mass effect of an intracavitary tumor can obstruct the transfer of blood through the cardiac chambers or can interfere with the normal coaptation and opening of the cardiac valves (*Figure 4.1*). Depending which chambers or valves are involved, the patient may present with syncope, angina, dyspnea, edema, ascites, or any combination of murmurs indicative of valve stenosis or incompetence. In addition, neoplastic involvement of the myocardium may impede myocardial pump function resulting in a presentation of congestive heart failure similar to a cardiomyopathy.

Figure 4.1 *Transesophageal echocardiography. Reprinted with permission of the Italian Society of Cardiology. Large left atrial myxoma attached to the interatrial septum, prolapsing in diastole through the mitral valve. From Basso C, et al., Cardiac Tumor Pathology, 2013.*



Pulmonary Hypertension

Elevated pulmonary artery pressures can be caused by obstruction of the pulmonary arteries by tumor emboli, but more commonly is a result of pulmonary venous hypertension due to obstruction to left heart filling.

Embolization

Systemic emboli from left heart lesions, in particular left atrial myxoma, are much more frequentl than pulmonary tumor emboli from right heart lesions.

Arrhythmia

Atrial fibrillation, one the most important arrhthmia Atrium may be a direct manifestation of primary neoplasms, metastatic cardiac tumors or tumors of adjacent tissues, such as the lungs and esophagus that invade the heart (3). Certain patients with cardiac tumor manifest only recurrent supraventricular or ventricular arrhythmias, most likely due to the irritative effect of tumor invading cardiac muscle. More rarely, the conduction system is injured resulting in heart block and Stokes-Adams attacks.

Chest Pain

Pain is a common manifestation of malignant tumors, but instances of ischemic cardiac pain due to tumor embolization to the coronary arteries (4) or extrinsic compression of myocardial vessels have been also reported (5).

Constitutional Symptoms

Fever, malaise, weight loss, Raynaud's phenomenon, hyperglobulinemia and an elevated erythrocyte sedimentation rate have all been described in both benign and malignant lesions but most frequently are associated with left atrial myxomas. The etiology of these phenomena is speculative. The leading theories postulate either an autoimmune or a systemic response to altered serum proteins damaged by tumour movement and to tumor breakdown products released into the circulation because of necrosis or hemorrhage. The hyperglobulinemia is always polyclonal and is completely reversible after tumor resection (6). There are no qualitative, just quantitative serum protein abnormalities. The elevated globulins probably explain the concomitant elevated erythrocyte sedimentation rate.

Hematologic Abnormalities

The hemolytic anemia and thrombocytopenia, again often noted in left atrial myxomas, are plied to be due to the mechanical destruction of these blood elements by a mobile intraluminal tumor (7). Polycythemia is seen on occasion with right atrial tumors and most likely represents the response to hypoxia when the tricuspid valve is obstructed with subsequent elevation of right atrial pressure, stretching of the foramen ovale, and right to left shunting (8).

4.1 Common Clinical Manifestations of Benign tumors

Patients are frequently asymptomatic and the tumor is found as an incidental finding on two-dimensional echocardiography.

When symptoms are present, dyspnea, especially dyspnea that is worse while lying on the left side, should alert to the possibility of a myxoma. Most signs and symptoms related to myxoma result from obstruction of the mitral valve (syncope, dyspnea, and pulmonary edema), followed by embolic manifestations (9). Patients may also have nonspecific symptoms such as fatigue, cough, low-grade fever, arthralgia, myalgia, weight loss, and erythematous rash, as well as laboratory findings of anemia, increased erythrocyte sedimentation rate, and increased C-reactive protein and gamma globulin levels. Less commonly they may have thrombocytopenia, clubbing, cyanosis, or the Raynaud phenomenon.

Findings on physical examination can reveal a systolic murmur or a diastolic murmur suggestive of mitral stenosis. A tumor plop may also be present (a low-pitched diastolic sound heard as the tumor prolapses into the left ventricle). In one study a cardiac auscultation abnormality was detected in 64% of the patients (10); the most common abnormal auscultation finding is a systolic murmur (in 50% of cases), followed by a loud first heart sound, an opening snap, and a diastolic murmur. A systolic murmur may be caused by damage to the valves, failure of the leaflets to coapt, or narrowing of the outflow tract by the tumor. A diastolic murmur is due to obstruction of the mitral valve by the myxoma. Tumor plop may be confused with a mitral opening snap or a third heart sound and can be detected in up to 15% of cases (10).

Chest examination may reveal fine crepitations consistent with pulmonary edema.

Examination of the extremities may also reveal signs of an embolic phenomenon and the signs vary depending on the vascular territory. Involvement of the cerebral vessels results in neurologic signs, involvement of the coronary arteries may result in an acute coronary syndrome, intestinal arterial

obstruction may result in an ischemic bowel, and peripheral arterial obstruction can result in limb-threatening ischemia.

4.2 Common Clinical Manifestations of Malignant Tumors

Malignant primary cardiac tumors commonly cause symptoms by three separate mechanisms: obstruction, embolization, and arrhythmias. Pericardial invasion and tamponade may be rarely the first manifestation of the disease. Both atrial and ventricular tumors, when large enough, may result in obstructive symptoms and cause syncope, chest pain, dyspnea, or heart failure.

The most common initial symptom is dyspnea, followed by chest pain, cough, syncope, hemoptysis, sudden death, fever, embolic events, and cardiac arrhythmias (11). Tumors infiltrating the ventricular wall might damage the myocardium or conduction system and result in ventricular arrhythmias. Conduction disturbances caused by myocardium invasion would lead to arrhythmia, such as premature beats or atrial fibrillation (12).

Large tumors on the right side, in addition to causing venous congestion, may also limit cardiac filling and result in sudden decreases in intravascular volume, thereby potentially precipitating syncope in these patients. Left-sided cardiac tumors, if large enough, can also impair ventricular filling and lead to syncope or heart failure.

Unfortunately, approximately 29% of cardiac sarcomas are found to have metastatic disease at initial evaluation, typically in the lung (11). Sarcomas, especially left-sided ones, are commonly associated with cardiac embolic events, (13) and arrhythmia can be an important problem as well. A finding of a cardiac mass with pericardial effusion should raise suspicion for a malignant cardiac tumor (14). It might be expected that the pericardial effusion associated with a malignant primary tumor is due to associated pericardial involvement; however, a malignant effusion is not always present.

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CHAPTER 5

IMAGING

Cardiac masses frequently present significant diagnostic and therapeutic clinical challenges. In many cases a cardiac mass is detected as an incidental finding and the resultant evaluation may culminate in confirmation of a cardiac tumor, which generally is an uncommon event because other cardiac masses, such as thrombus or vegetation, are generally much more common.

5.1 Initial Decision Making

It is interesting to note that patients with cardiac tumors may initially have no symptoms or physical findings but exhibit abnormalities on imaging. Alternatively, there may be a host of nonspecific symptoms or findings on physical examination, and of course, there may be very specific and detailed symptoms or signs that should alert physicians to the possibility of a cardiac tumor (*Table 5.1*) (1,2). The most important consideration in confirming the presence of a cardiac tumor is a high index of suspicion and integration of the symptoms, findings on physical examination, and imaging characteristics in a logical way to establish a clinically reasonable plan of action. Primary tumours of the heart and pericardium may be detected as an abnormal finding on a chest radiogram or another imaging test obtained for an unrelated reason. Taking into account the likelihood of cardiac tumors the diagnostic procedures should be performed in all patients with unexplained cardiac murmurs, congestive heart failure, arrhythmias, which are accompanied fever, anemia and weight loss of unknown cause. In such cases the basic laboratory tests should include tumor markers. Cardiologic diagnostic procedures should be widened with particular emphasis on imaging methods.

Table 5.1 *Range of clinical findings that may indicate a cardiac tumor. Modified from Braunwald's Heart Disease, 2015.*

Clinical findings that may indicate a cardiac tumor
Completely asymptomatic but an incidental abnormality on imaging
Low-grade fevers
Transient ischemic attack or cerebral vascular event
Positional dyspnea
Weight loss
Peripheral embolic events
Chest discomfort
Congestive heart failure
Upper extremity or neck swelling
Lower extremity venous thrombosis
Palpitations
Arrhythmias
Pericardial effusion/tamponade

Once detected, cardiac imaging is needed to define tumour location, extent and boundaries; relationships with adjacent key cardiac structures such as valves and coronary arteries; tumour type; and presence and degree of functional impairment.

The initial evaluation is typically an imaging test such as two-dimensional echocardiography (3) or magnetic resonance imaging (MRI) (4) by which a mass is identified. Depending on the characteristics of this mass and the known comorbid conditions of the patient, additional imaging may be undertaken, including three-dimensional echocardiography with contrast enhancement (5), MRI with gadolinium (6,7), coronary angiography to define the presence of coronary artery disease (8), position emission tomography (PET) to provide staging for cancer, or computed tomography (CT) to clarify intrathoracic structures (9,10). Transesophageal echocardiography (TEE) can also provide very specific anatomic information that is critical to planning treatment (8) (*Table 5.2*).

Table 5.2 *Common testing that may indicate the possibility of a cardiac tumor. Modified from Braunwald's Heart Disease, 2015.*

Imaging Test
Two- or Three-dimensional echocardiography
Chest radiography
Computer tomography
Magnetic resonance imaging
Transesophageal echocardiography
Position emission tomography
Nuclear scintigraphy

When assessing a cardiac mass as initial evaluation for a cardiac tumor, the clinical context in which the image was obtained is critical because the differential diagnosis of a cardiac mass is broad and includes tumors, thrombi, infection, and artifacts (*Table 5.3*).

Table 5.3 *Differential diagnosis of cardiac masse. Modified from Braunwald's Heart Disease, 2015.*

Differential Diagnosis
Intracardiac thrombus
Focal myocardial hypertrophy
Left ventricular noncompaction
Infectious (abscess)
Primary cardiac tumor
Secondary cardiac tumor (metastasis)
Lipomatous hypertrophy of the septum
Cyst
Imaging artifact

For example, if two-dimensional echocardiography shows an apical mass in a patient with new-onset heart failure, a cardiac tumor is less likely (11). The presence of a severe wall motion abnormality, as well as the fact that the mass may appear distinct from the myocardial wall and is lobulated, strongly suggests that the mass is much more likely to be a thrombus than a tumor (*Figure 5.1*). Another scenario involves a patient with a history of melanoma that is metastatic to other organs and on routine cardiac imaging a solid mass is seen in an unusual location. Because there is no wall motion abnormality and no significant valvular disease or clinical signs suggestive of infective endocarditis, this mass is very likely to be a metastatic lesion to the heart (*Figure 5.2*).

Figure 5.1 *Transthoracic color-Doppler echocardiography. Vascularized apical thrombus. Upper panel: epicardial tract of the left anterior descending (LAD) coronary artery visualized by color-Doppler and the corresponding pulsed Doppler tracing with the characteristic anterograde systolic and diastolic flow. Lower panel: vascularized apical thrombus with flow directed away from the transducer. From Basso C, et al., Cardiac Tumor Pathology, 2013*

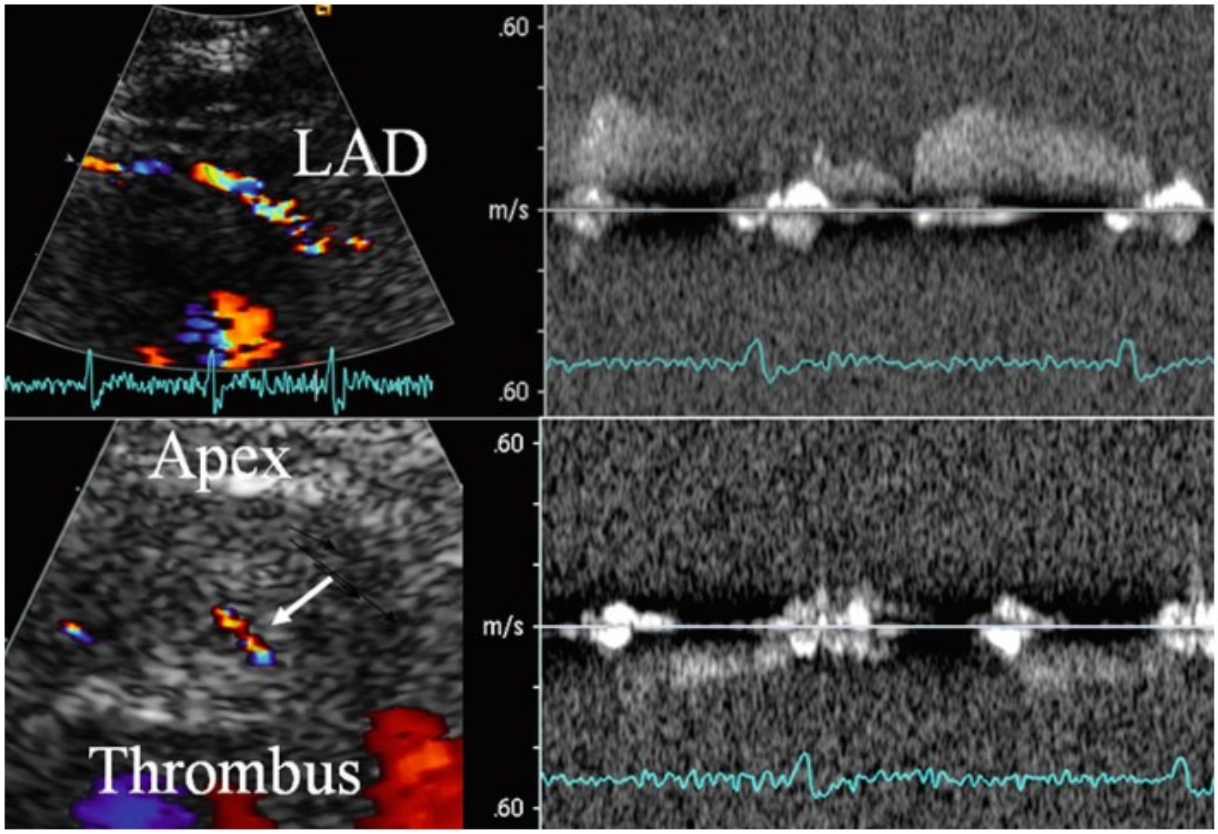
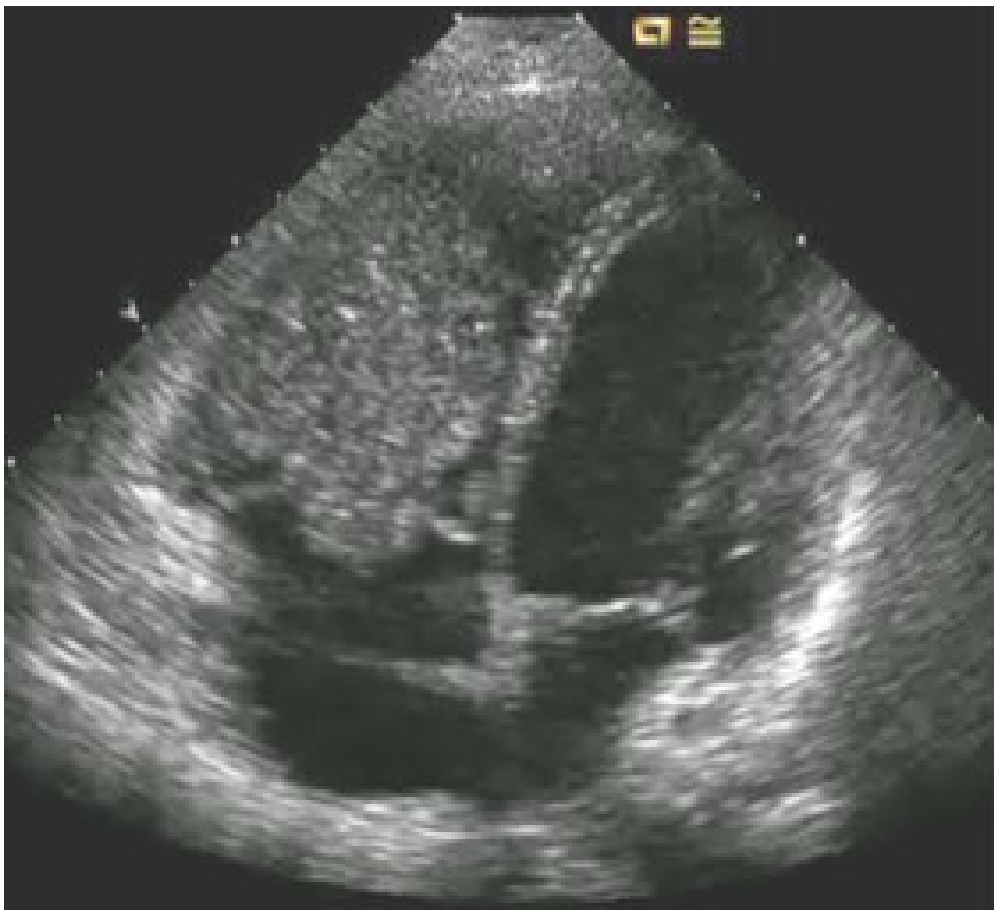


Figure 5.2 *Two-dimensional echocardiography, apical four-chamber projection. Reprinted with permission of the Italian Society of Cardiology. Metastatic melanoma infiltrating almost entirely the right ventricle, and prolapsing in systole through the tricuspid valve. From Basso C, et al., Cardiac Tumor Pathology, 2013*



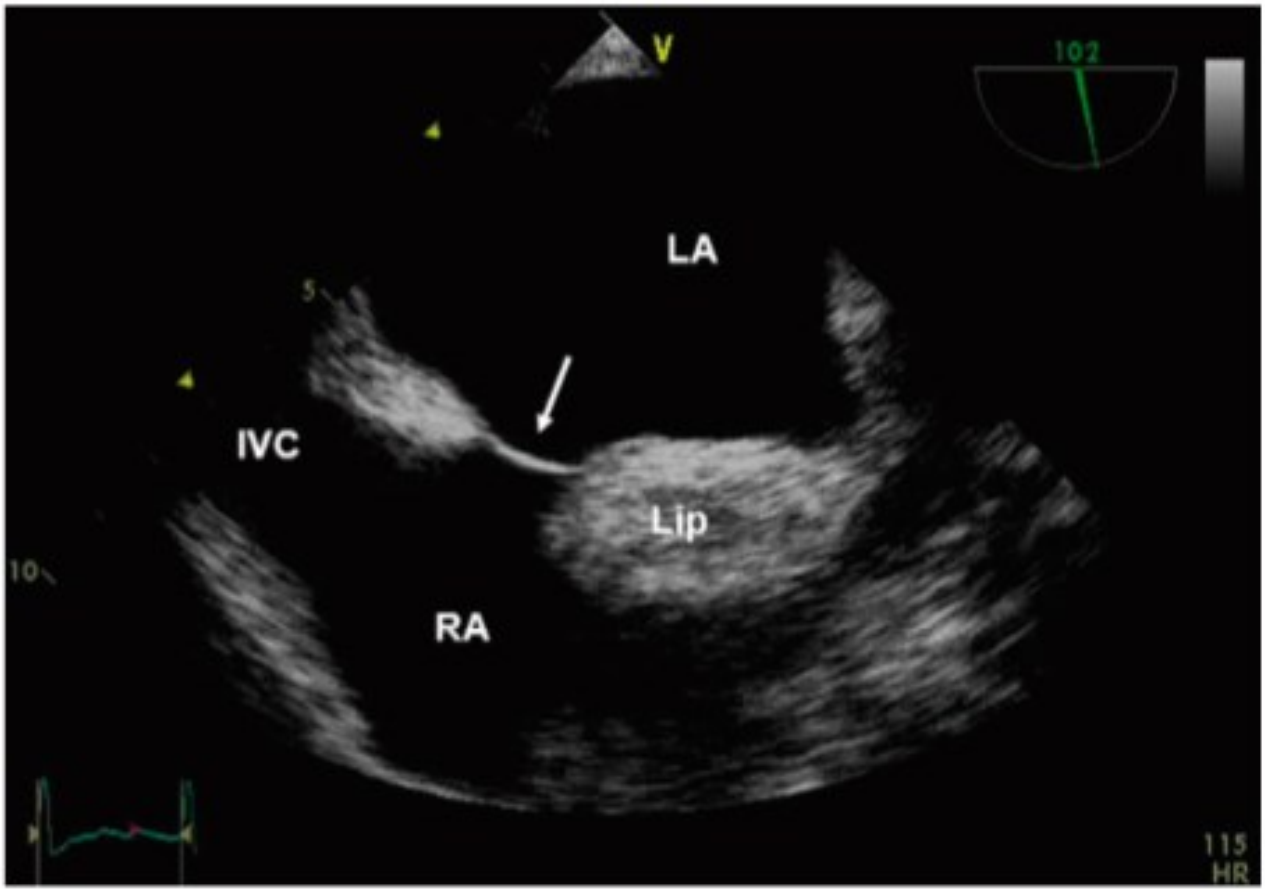
A common consideration that may suggest a tumor, in regard to imaging, is movement of the mass and related structures during a motion image. If a tumor is infiltrating the myocardium, the involved myocardial area will not contract in normal fashion. A left ventricular myocardial apical mass contracting similar to that of surrounding tissue is likely to be either focal hypertrophy or left ventricular noncompaction (12,13) as opposed to a cardiac tumor.

Furthermore, progression of an image over time may also indicate the pathologic process. If a cardiac mass changes in size from one image to the next, suspicion of a cardiac tumor is much higher. However, if an apical mass is stable for months or years, it is very unlikely to be a cardiac tumor. Of course, the exact nature and location of a mass are critical in determining whether it is

likely to be a tumor (14). A classic example of this principle is lipomatous hypertrophy of the intra-atrial septum (*Figure 5.3*). The initial suspicion might be a myxoma or other tumor, but TEE revealing specific characteristics that are a hallmark of lipomatous hypertrophy will confirm the diagnosis (15,16).

The main non-invasive imaging modalities for evaluating primary cardiac tumours each have advantages and disadvantages. They are often used together in a complementary manner for diagnosis and surgical planning (17).

Figure 5.3. *Lipomatous hypertrophy of the interatrial septum. Transesophageal echocardiography shows the typical thickening of the interatrial septum (Lip) that spares the region of the fossa ovalis (arrow) giving the classic dumbbell appearance to the interatrial septum. From Basso C, et al., Cardiac Tumor Pathology, 2013*



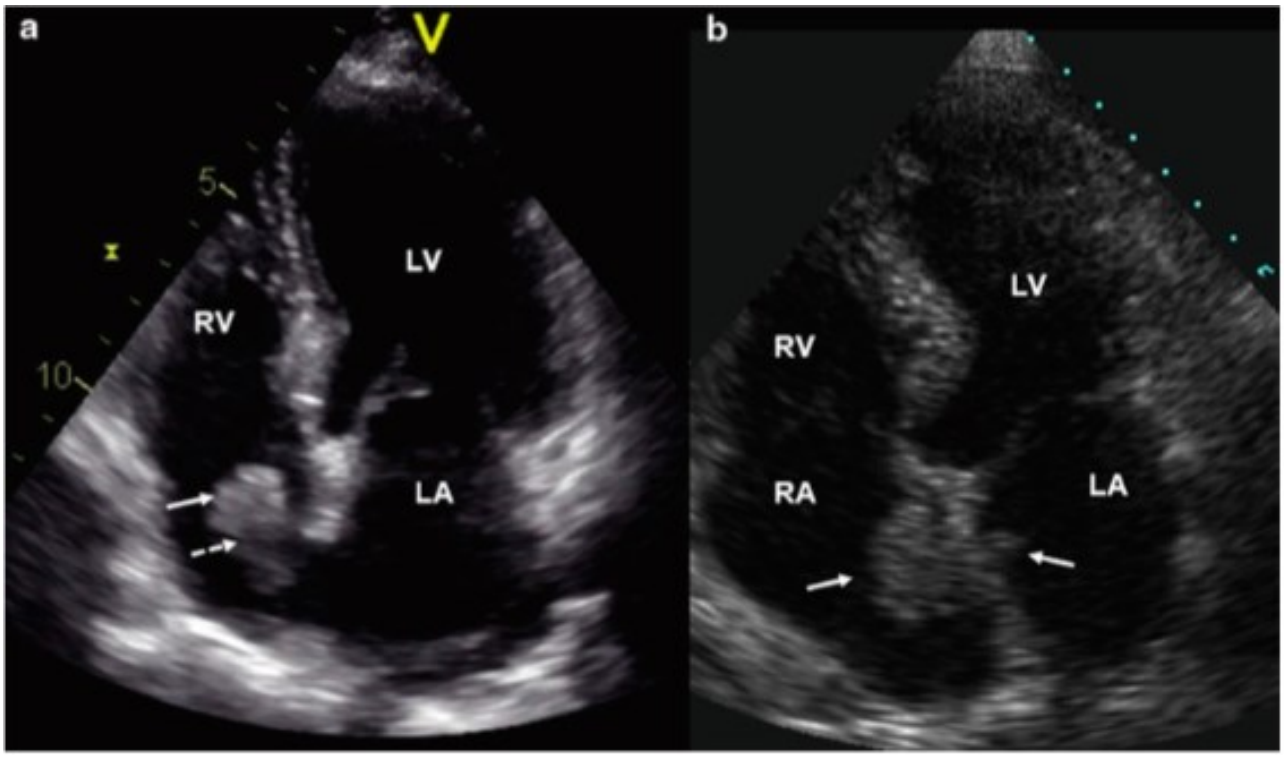
ECG may not indicate any change, and some ECG features found in patients with cardiac tumor are usually nonspecific. It has been reported, that tumors of the heart are associated with shortening of P-R interval, the right or left bundle branch block (RBBB or LBBB) or complete heart block (18). There may also occur recurrent supraventricular tachycardia (19).

Standard chest radiography may not reveal any changes. Uncharacteristic enlarged heart contour following a tumor appears in connection with heart failure. Asymmetrical enlargement of the heart may occur when the tumor is located within the anterolateral wall of left ventricle. Calcifications are rare, usually in the case of myxoma or fibroma. Pericardial effusion as the only radiological indicator of cardiac tumor (19,20).

5.2 Echocardiography

The primary advantage of echocardiography is that it has the best spatial and temporal resolution and provides excellent anatomic and functional information (21). It is the optimal imaging modality for small masses (<1 cm) or masses arising from valves (*Figure 5.4*)(22). A second major advantage of echocardiography is the ability to image velocities with Doppler, which allows for assessment of presence, degree, and location of obstructions to blood flow or valve regurgitation. Echocardiography is typically the modality used for the initial evaluation of cardiac tumours and may be the only diagnostic test required in some patients. Disadvantages include suboptimal image quality in patients with poor acoustic windows, inability to image extent of disease outside of the mediastinum, and relatively low soft tissue contrast, which limits detection of tumour infiltration and characterization of tumour tissue. Also, intravenous contrast agents are not routinely used with echocardiography, which limits the ability to characterize tumour vascularity (23). Although transthoracic echocardiography is simpler quieter and usually can identify a tumor, transesophageal echocardiography (TEE) may be more informative.

Figure 5.4 *(**a**) A large right atrial myxoma attached to inter-atrial septum. Areas of calcification (arrow) and echolucencies (dashed arrow) can be appreciated within this polypoid mass. (**b**) A large right atrial mass (arrow) attached to the interatrial septum, associated with a second smaller mass attached to the left side of interatrial septum (arrow), that were found to be myxomas at pathological examination. LA left atrium, LV left ventricle, RA right atrium, RV right ventricle. From* Basso C, et al., Cardiac Tumor Pathology, 2013.



The superior diagnostic utility of TEE is due to the proximity of the esophagus to the heart, the lack of intervening lung and bone, and the ability to use high-frequency imaging transducers that afford superior spatial resolution (24). Fetal echocardiography allows for early diagnosis of cardiac embryonic tumor (25).

5.3 Magnetic Resonance Imaging (MRI)

The primary advantage of MRI is its excellent soft tissue contrast which makes it the most sensitive modality for detection of tumour infiltration. MRI has more manipulable imaging parameters than other imaging modalities. Because of this, MRI is the best modality for characterizing tumour

tissue. For example, a T2-weighted standard or fast spin echo sequence distinguishes tumours with high water content, such as haemangioma, from tumours with low water content, such as fibroma. A third advantage of MRI is the ability to characterize tumour vascularity with intravenous contrast. Though not as flexible as echocardiography, MRI does allow assessment of wall motion and assessment of velocities through large vessels. This allows for characterization of ventricular function, inflow or outflow obstruction and valve regurgitation. The primary disadvantage of MRI is long examination times, which translates into the need for sedation in children, and the need for reliable ECG gating. MRI should be considered when the tissue type, exact location, or the relationships of the tumour with neighbouring structures are not completely defined by echocardiography and when surgical resection of the tumour is considered (26-28).

5.4 Computed Tomography (CT)

ECG gated CT scans with the latest generation of multidetector scanners or with electron beam scanners are also very useful for cardiac imaging. In many ways, the advantages and disadvantages of CT are intermediate between those of echocardiography and MRI. Modern CT scanners have excellent spatial resolution, which is better than that of MRI, but not as high echocardiograpy. CT has better soft tissue contrast than echocardiography, and can be used to definitively characterize fatty content and calcifications; however, the overall soft tissue contrast and ability to characterize tumour infiltration and tumour type is less than that of MRI. Intravenous contrast can provide information about tumour vascularity, an advantage CT shares with MRI. CT may be used as an adjunct to both echocardiography and MRI. Positron emission tomography (PET) may be useful in identifying cardiac involvement in patients with metastatic tumors, atrial myxoma, or lipomatous septal hypertrophy (29-31).

5.5 Cardiac Angiography

Coronary angiography is performed to assess the vascularity the tumor and its infiltration of the coronary arteries. This is of a particular importance in making the decision about surgery and the choice of it's techniques. Cardiac catheterization provides additional information about the hemodynamic consequences of the presence of the tumor of the heart (32).

Angiography provides indirect and nonspecific imaging based on filling defects within the cardiac chambers and displacement of the coronary arteries (32). Two exceptions are worth noting. First, endomyocardial biopsy for tissue typing may be considered in selected patients. Second, selective coronary angiography is helpful when planning surgical resection of an intramyocardial tumour.

5.6 Transvenous Endomyocardial biopsy

Intracardiac tumors are generally diagnosed by transthoracic echocardiography, transesophageal echocardiography and, more recently, magnetic resonance imaging. However, these techniques do not permit a histopathologic diagnosis. When surgery is not indicated because of limited hemodynamic changes but the benign nature of the tumoral mass is questionable, percutaneous transvenous biopsy, when technically feasible, may represent an alternative approach (33). The first reported use of TEE-guided intracardiac biopsywas by Scott and associates (34). A mass was embedded within the posterolateral wall of the right atrium, adjacent to the tricuspid annulus, and a percutaneous right femoral vein approach was used. This transvenous endomyocardial biopsy have the limit that are data available on the risks and benefits of transvenous biopsy of suspected cardiac tumors. Because myxomas may embolize, transvenous biopsy is not generally warranted if the appearance is typical on noninvasive imaging. Biopsy is considered reasonable for other cardiac tumors if potential benefits are deemed sufficient to outweigh potential risks.

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CHAPTER 6

BENIGN PRIMARY CARDIAC TUMORS

Most (about 90%) primary cardiac tumors are benign, (1-7). Myxoma constitutes about 70-75% of all benign cardiac tumors in adults, but only a small percentage of such tumors in children (4). Rhabdomyoma is reported as the most common benign tumor in children (4,5). Other benign cardiac tumors that have been described include fibromas, lipomas, hemangiomas, papillary fibroelastomas, cystic tumors of the atrioventricular node, and paragangliomas.

6.1 Cardiac Myxoma

Cardiac myxomas represent the most common primary cardiac tumors (1,2,6-11). They are mainly localized to fossa ovalis on the left atrium and in up to 5% of cases overriding it and apparently looking as a biatrial tumor (10,11). Cardiac myxomas are usually single tumors, but rarely they can be multiple and familial as part of Carney complex (12-18).

They have uncertain histogenesis and show a wide range of clinical presentations that may mimic a variety of neoplastic and nonneoplastic conditions (19-21). The tumor characteristics, together with possible tumor relapse following incomplete surgical resection, have contributed to the controversial issue of malignant myxomas or metastatic potential of cardiac myxomas (22,23). Several histological, cytogenetic, and molecular studies have been investigating their pathological and biological characteristics, including mechanisms of growth and embolic potential, and increasing evidences are confirming the benign byology of cardiac myxoma. Modern histological criteria and diagnosis tools (i.e. immunohistochemistry and molecular biology) are helpful for differential diagnosis from myxoid sarcomas that may share similar gross features but have malignant behavior and often poor prognosis (22,23).

Epidemiology

Myxoma show a female preponderance, with F/M ratio of 1,8/1, a mean age at diagnosis of 50 years, most patients being in 30-60 age range (10, 22, 24). Nevertheless they are reported also in pediatric age, and as a part of a genetic disease (i.e. Carney complex), diagnosed in young patients without sex predilection (14-18, 25).

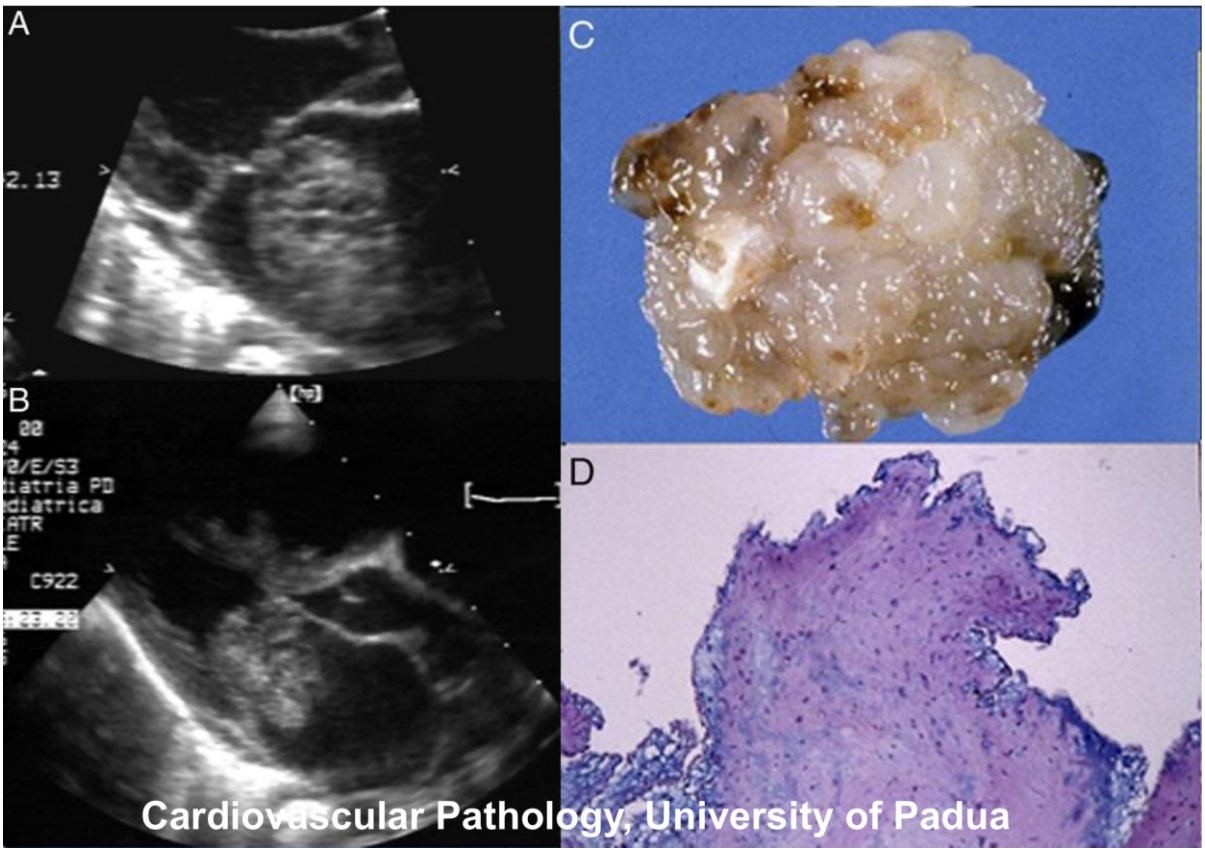
Macroscopy and histopathology

Cardiac myxomas are intracavitary masses that occur most often in the left atrium (*Figure 6.1*). They arise from the endocardium of the atrial septum near the fossa ovalis in 85-90% of cases. Most of the remainder is located in the right atrium. Rarely, they arise in the ventricles.

Multiple tumours occurring at sites other than fossa ovalis and ventricles are generally found in the inherited form of cardiac myxoma. Very rarely cardiac myxomas have also been documented to occur on valves and chordae tendineae.

The external appearance, consistency, size and weight are extremely variable. They may be as small as a few millimeters and as large as 14 cm in diameter. The weight ranges are from 2-250 gm. Tiny cardiac myxomas may be totally asymptomatic and discovered incidentally at surgery for another purpose or autopsy. Larger ones are either sessile or pedunculated, but the site of attachment is always discrete and usually in the region of the fossa ovalis. Occasionally, the stalk may be long, resulting in free mobility of the tumour within the atrial cavity.

Figure 6.1 *Left atrial endocavitary mass (A and B) Two-dimensional echocardiography, parasternal long-axis view (systole and diastole): note the diastolic tumour prolapse and the left atrial mass attached to the fossa ovalis; (C) gross examination of the surgically resected mass: note the polylobulated, myxoid appearance variegated in colour; (D) histology: note the typical villous appearance with stellate cells in a myxoid background, in keeping with a diagnosis of myxoma. From Basso et al., Heart, 2016.*



Myxomas are ovoid, globular, lobulated or polypoid. They may be smooth and glistening or have multiple papillary, villous, finger-like projections. They may be grey white and fibrous, gelatinous and myxoid, or a combination of both. The papillary structures may be quite friable increasing the risk of embolisation. Superficial thrombi also embolize. Marked variation in colour is distinctive. Pale grey, pearly white or yellow brown areas are frequently admixed with haemorrhagic dark brown or red areas. Tumour consistency depends on the quantity and distribution of fibrous tissue, and calcification. Rarely, the bulk of the tumour becomes calcified, so-called lithomyxoma (26).

Histologically, cardiac myxoma is made up by a mucopolysaccharide-rich matrix conferring the typical myxoid aspect and numerous thin-walled blood vessels together with characteristic myxoma

lepidic cells. indicating (see ancient Greek lepis term) the scale-like cell shape. Lepidic cells are stretched or star-shaped, showing round or oval nucleus with often evident nucleolus. They may be single, scattered cells or they constitute small nests, cord-like or perivascular structures. Perivascular structures are made up of single or multiple lepidic cell layer/s surrounding a central lumen with endothelial lining, with alcian-blue amorphous substance deposits between the lepidic cell layers. Associated features consist of hemorrhage, extramedullary hematopoiesis, inflammatory infiltrates (made up of granulocytes, lymphocytes, plasma cells, macrophages, and hemosid- erin-laden macrophages), hemosiderin deposits, dystrophic calcifications (with possible Ghandi- Gamna sclerosiderotic areas and granulation tissue) and/or metaplastic ossification together with limited foci of necrosis. Calcifications may develop also within cell cords or pseudovascular cuffings, with characteristic stripe or ring shapes, both of them showing faded edges. Finally, the extracellular deposits of hemosiderin may develop a stretched structure, i.e., the so-called bamboo-shaped pattern. The myxoma pedicle is constituted by fibrous tissue with thick-walled vessels with possible medial and/or intimal hyperplasia. At tumor basis, myxoma may micrscopically infiltrate the adjacent endocardium and the underlying myocardium. Histologically, the infiltration is characterized by a stromal myxoid intercellular substance, which together with rare lepidic cells, pass through the cardiac myocytes and also in the medial arteriolar wall of the peduncle vessels (1,6). Within tumor, vessels of small and medium size (the latter ones usually are close to the base), and smooth muscle cells, localized to the media of blood vessels or in groups of cells interspersed in the myxoid stroma, are variably detected .

Histopathogenesis

The histogenesis of cardiac myxoma remains uncertain and different hypotheses have been formulated (27-29). This difficulty derives from the nature of morphological and immunohistochemical characterizations of this tumour. In fact, variable expressions of proteins typical of different adult cell phenotypes has been reported, even in the same cardiac myxoma,

suggesting an epithelial, endothelial, myogenic, myofibroblastic or neural origin (30-37). Phenotypic heterogeneity is also observed during cardiac development. In adult myocardium, two sarcomeric actins, α-cardiac (α-CA) and α-skeletal actin (α-SKA), are co-expressed and represent the predominant isoforms (38); in addition, α-smooth muscle actin (α-SMA) is transiently observed in cardiomyocytes during the early stage of fetal life (39). A possible explanation of heterogeneous differentiation in cardiac myxoma is the origin from a pluripotential cell or from a subendothelial vasiform reserve cell (28,29). Although some morphological homologies between cardiac myxoma cells and those of embryonic cardiac cushion cells may support this hypothesis, available data remain scarce and inconclusive (40). The two main hypotheses suggesting an origin from multipotent mesenchymal cells or from neural endocardial tissue (27-41,42). Their preferential site (i.e. foramen ovale) is considered to be consistent with an origin from multipotent mesenchymal cells or from embryonic rests (42-44). Kodama et al (45) show a cardiomyogenic derivation of cardiac myxomas based on the finding of transcripts for Nkx2.5/Csx, typical of the cardiac homeobox gene, and consistent with a primitive cardiomyocytic phenotype. Other Authors have shown distinctive patterns and gene expression compatible with endocardial neural or embryonic tissue origin (27,46). Finally, Orlandi et al. in order to define the origin of this tumour have investigated the phenotype of cardiac myxoma cells in a large series of consecutive tumours with reference to the expression of actin isoforms and possible aspects of vascular differentiation. They reported the expression in tumour cells of transcripts characteristic of cardiac cushion development and/or primitive cardiac mesenchymal differentiation (27).

Neoplastic theory

Cardiac myxoma is actually considered a neoplasm. It is histologically distinct from thrombus that may mimic cardiac myxoma. Many evidences are supporting the neoplastic hypothesis, either by showing a definitive pattern of differentiation, on the basis of cytological, ultrastructural, and immunohistochemical features, or demonstrating the biological characteristics by using experimental models such as in vitro cell cultures comparing thrombus and cardiac myxomas (47-49).

Thrombotic theory

Development of cardiac myxomas from thrombus has been hypothesized (50). Myxomas apparently have show growth rate as mural intracardiac thrombus, often are partially covered by thrombotic depositions (similar to Lambl excrescences at gross examination) and share common features with organized thrombus (51). However, cardiac myxomas are characterized by the typical neoplastic lepidic cells and by a well-defined vascularization.

Dysembryoplastic theory

Cardiac myxoma has been supposed to represent a hamartoma originating from endocardial embryonic myxoid rests localized to foramen ovale (9). However, they are not present a birth, being usually diagnosed late in life, and do not spontaneously regress (12,13).

Histopathogenesis of glandular cells in myxoma

Glandular structures may be rarely found within an otherwise typical cardiac myxoma. Morphological and immunohistochemical studies support two hystopathogenetic hypotheses, that is a possible origin from embryonic foregut rests (52,53) or a progressive differentation from neoplastic multipotent myxoma cells (22). During the embryonic development, the foregut, and the primitive heart tube lie adjacent and the same area as most cardiac myxomas, i.e. foramen ovale, therefore glandular foregut rests might result to be embedded within myxoma, althongh embryonic glandula structures have never been described in the atrium septum so far.

Genetics

The chromosomal patterns of sporadic cardiac myxoma are characterised by extensive intratumour heterogeneity. In the cases published to date, multiple unspecific chromosome aberrations have been reported, including dicentric chromosomes and, in particular, telomeric associations. Intratumour heterogeneity, as found in a variety of tumour types and grades, is considered a sign of genetic instability presumably resulting from disruption of genes that control genomic integrity. Studies of cardiac myxomas suggest that the chromosomal regions 12p1 and 17p1 may play a specific role in the development of these neoplasms since they are frequently rearranged.

Whether there is a common genetic mechanism underlying sporadic and familial cardiac myxomas is unclear. Based on linkage analysis, 2 loci have been proposed for genes causally related to the myxoma syndrome: 2p16 and 17q2. A gene located at 17q24 was cloned that showed mutations in myxoma patients. This gene, PRKAR1A, represents a putative tumour suppressor gene, coding for the type 1 alpha regulatory subunit of protein kinase A, found in Carney syndrome. Neither mutations of PRKAR1A nor loss of heterozygosity of markers at 17q2 and 2p16 have been found in sporadic cardiac myxomas (54,55).

Flow cytometry shows abnormally high tetraploid DNA patterns in all cases of syndromic myxomas, whereas in sporadic myxomas it is present only in about 20%.

Genetic susceptibility

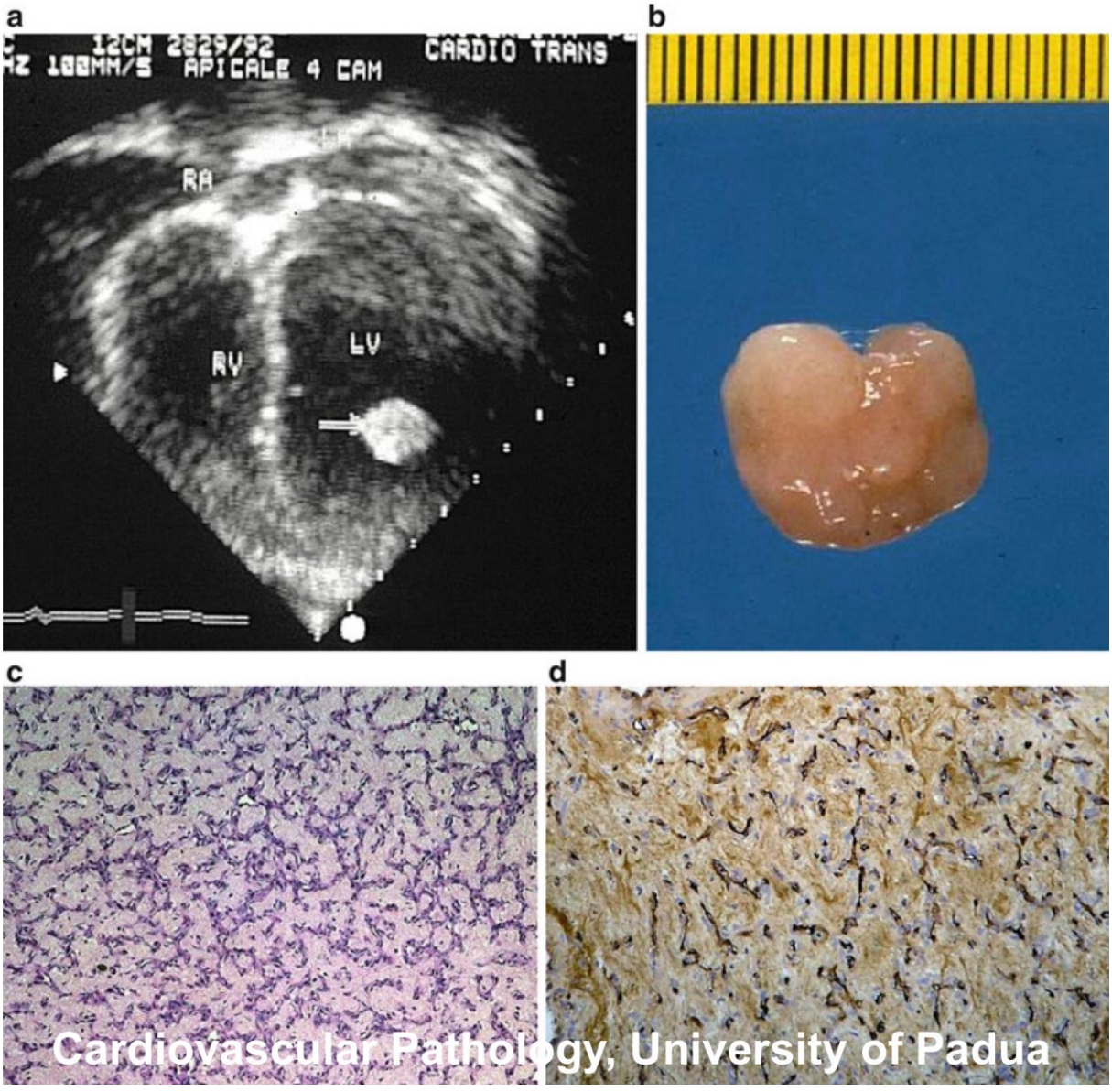
Although most myxomas are sporadic, some have been associated with the myxoma complex. This autosomal dominat syndrome has been reported under the acronyms NAME (nevi, atrial myxoma, myxoid neurofibroma, ephelides), LAMB (lentigines, atrial myxoma, mucocutaneous myxomas, blue nevi), and more recently as Carney syndrome (14-18). This syndrome includes cardiac myxomas and extracardiac manifestations: abnormal skin pigmentation (lentigines and blue nevi), calcifying Sertoli-Leydig testicular tumours, cutaneous myxomas, myxoid breast fibroadenomas, pigmented adrenal cortical hyperplasia, pituitary hyperactivity, psammomatous melanotic

schwannoma and thyroid tumours. Familial myxomas are estimated to account for 7% of atrial myxomas, are more often multiple, recurrent and right sided, as compared to sporadic myxomas. The affected patients are also younger, most presenting at 20-30 years of age.

Differential Diagnosis and Peculiar Clinical Aspects

Differential diagnosis of intracardiac myxoid masses requires hystology. Myxoid tumors of the heart may correspond to biologically benign myxoma, to myxoid sarcomas, or even to cardiac metastasis (56-58). The presence of myxoid stroma is not a pathognomonic feature and diagnosis of myxoma requires the presence of lepidic cells and the absence of mitosis. Hemorrhage, hemosiderin deposits, and inflammatory cells are frequently found in myxomas but are not specific (*Figure 6.2*). Base infiltration may be microscopically observed in myxomas, whereas in sarcomas and malignant tumors it is often quite extensive and grossly evident (6-9). Few report have raised to controversial issue whether malignant variants of cardiac myxomas with metastatic potential do exist (23). The metastatic potential of cardiac myxoma might rather correspond to clinical consequences of tumor embolism and depend upon morphology of tumor, soft consistency, thrombotic depositions on the tumor surface and hemodynamic forces that may cause detachment of even conspicuous tumor fragments with embololism and even occlusion of pheripheral arteries causing ischemic damage of organs or tissue (19,20,22). Cardiac myxomas do not show a correspondent malignant countepart, and myxosarcoma is not a recognized entity in the present WHO classification of cardiac tumors (2).

Figure 6.2 *A 20-year-old patient with a small left ventricular apical mass. (a) Two-dimensional echocardiography, apical four-chamber view shows a round mass at the left ventricular apex (arrow) (LA left atrium, LV left ventricle, RA right atrium, RV right ventricle). (b) Gross view of the surgically resected mass: note the smooth surface and the pink color. (c, d) At histology and immunohistochemistry, the benign proliferation shows a myxoid background with vessel proliferation in keeping with myxomatous angioma (hematoxylin–eosin and CD31. From Basso et al., Circulation, 1998.*



6.2 Papillary Fibroelastoma (or Papilloma)

Definition: An endocardial based papilloma lined by endothelial cells with proteoglycan and elastin rich avascular stroma.

Papillary fibroelastoma (PFE, also know as endocardial fibroelastic papilloma or giant Lambl excrescence) represents the second most frequent benign lesion after cardiac myxoma, excluding pericardial cyst (1,2,6,46,49,50,52). While in the past it was mostly an incidental autoptic obsevation, an exponential increase of clinically diagnosed PFEs occured in the last 20 years due to the wide-spread use of two-dimensional trans-thoracic and trans-esophageal ecocardiography, even in asyntomatic patients (59). The true incidence is difficult to determine, as the tumour may be overlooked and there is morphologic overlap with Lambl excresences, a reactive age-related valvular lesion. In recent series of surgically excised cardiac tumours papillary fibroelastoma represents the second most frequent benign lesion (6,59).

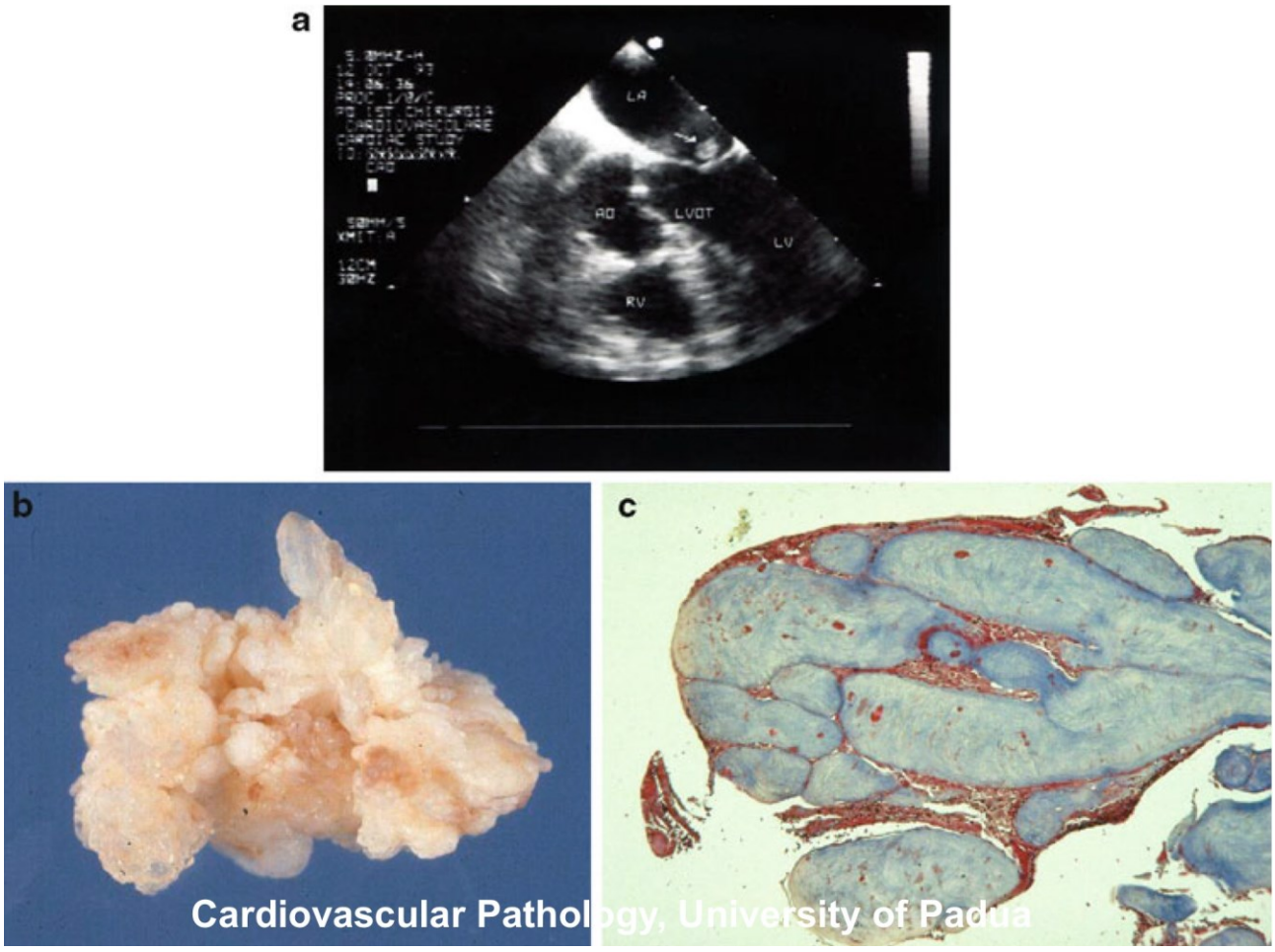
Papillary fibroelastoma is the second primary cardiac tumour following myxoma in Padua series (8%) (1,6) and it is the most common primary heart valve tumour (60-62) (*Figure 6.3*). It is predominant in the 4th and 5th decades of life and in males (63).

Localization

Gowda et al. reviewed 725 cases of cardiac papillary fibroelastoma reported in the literature, and found that the valvular endocardium was its predominant location (63). More than 95% arise in the left heart, including aortic (29%), mitral valve leaflets, mitral chordae and papillary muscles (25%). Unusual locations include the tricuspid (17%) and pulmonary valves (13%),, but also the mural non-valvular endocardium may be the site of growth, in the latter case being difficult to differentiate from thrombus and myxoma (60-66). On gross examination, it is a small intra-cavitary neoplasm usually single, firm, with a short pedicle and multiple papillary fronds similar to a sea anemone

when under water (1,6). This tumors are found most commonly (69.5%) on diseased valves, 37.8% post-rheumatic valves and 62.2% valves with fibrosis and calcification. Papillary fibroelastomas have been likened to Lambl excrescence, but unlike Lambl excrescences, which occur at the line of closure of semilunar valves, papillary fibroelastomas occur anywhere on the valve surface (67). Left-sided lesions are much more frequently symptomatic (2).

Figure 6.3 *Papillary fibroelastoma of the mitral valve in a 74-year-old woman who underwent coronary artery bypass surgery. (a) Trans-oesophageal 2D echocardiography: a round mass, 5 mm in diameter, is visible on the atrial side of the anterior mitral valve lea flet (AO aorta, LA left atrium, LV left ventricle, LVOT left ventricular out flow tract, RV right ventricle). (b) Gross view of the resected mass, showing the irregular surface with variable color. (c) At histology,a fibrin network is visible within the fibroelastic fronds of the tumor (Heidenhain trichrome stain). From Basso et al., Heart, 2003.*



Macroscopy and histopathology

Papillary fibroelastomas range in size from 2-50 mm in greatest dimension, although the majority is less than 10 mm. They are generally opalescent white, but this colour may be obscured by thrombus. They are usually attached to the endocardial surface by a short single stalk, but those with more than one attachment to the endocardium have been observed. Papillary fibroelastomas have multiple papillary fronds and, particularly when immersed in water, they resemble a sea anemone. Papillary fibroelastomas most often occur singly (80-90%).

At histopathology, it is a papillary lesion with a thin layer of mucopolysaccharide matrix and avascular stroma composed predominantly of elastic fibres and a small amount of collagen, covered with a single layer of endothelial cells (65).

Recent or organised thrombi may be observed, entrapped within the fronds, having the potential to lead to thrombo-embolic events.

Surface endothelial cells express vimentin, CD34, CD31 and factor VIII related antigen (68).

6.3 Hemangioma

Definition

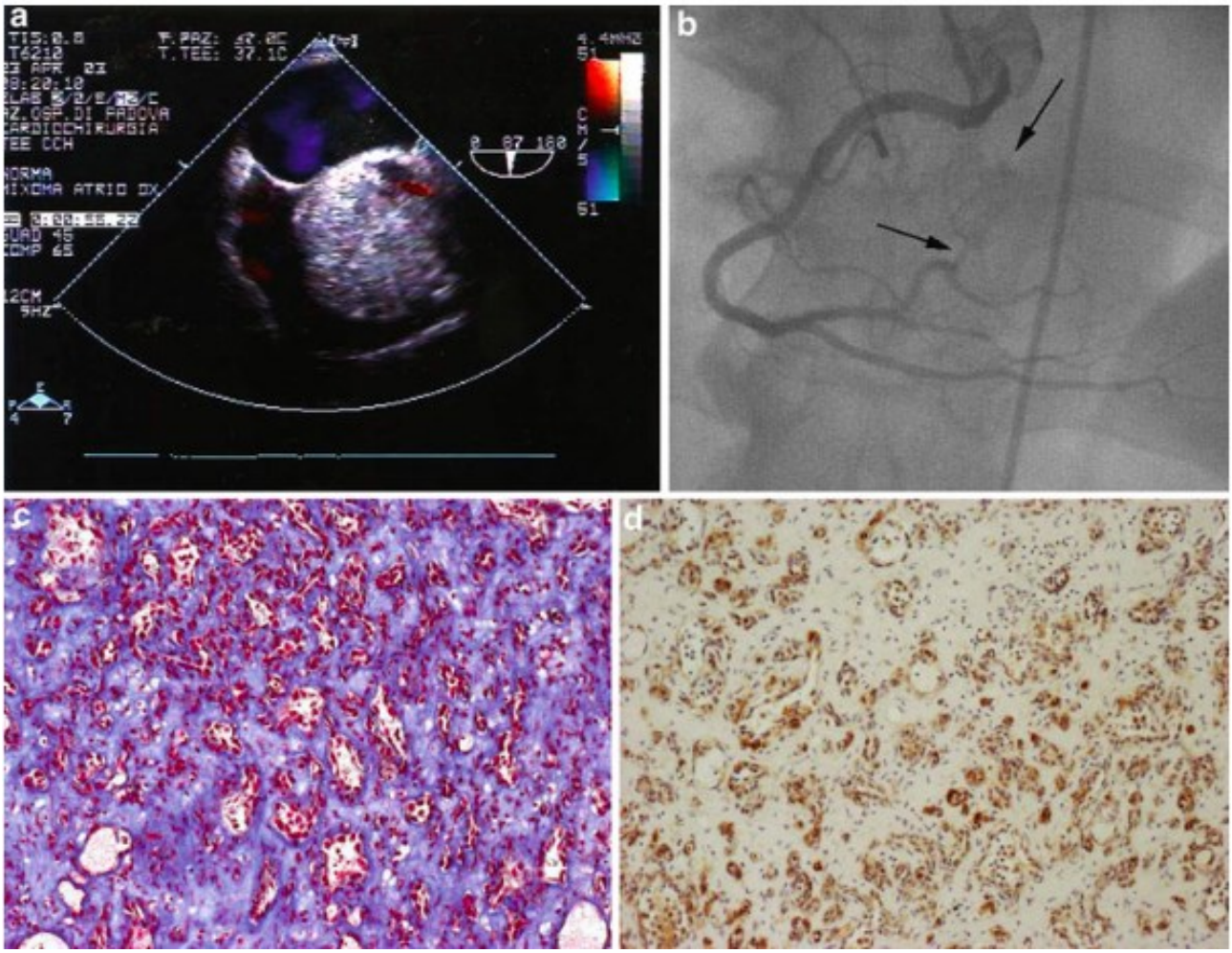
Haemangiomas are benign tumours composed predominantly of blood vessels. The histologic classification includes those composed of multiple dilated thin-walled vessels (cavernous type), smaller vessels resembling capillaries (capillary type), and dysplastic malformed arteries and veins (arterio-venous haemangioma, cirsoid aneurysm).

Haemangioma accounts for approximately 1 to 5% of all benign cardiac tumours in different series (1,2,69-73). It occurs mostly in adults, and the clinical presentation varies depending on the location and size of the tumour. A total of 75% present with an intramural growth and 25% are sessile or polypoid, projecting into the atrial or ventricular cavities, sometimes mimicking myxoma. Epicardial location is also reported. Coronary angiography may be useful in detecting the distribution of the afferent vessels to the tumour (*Figure 6.4*) (74). The histologic appearance is that of a proliferation of blood vessels lined by endothelial cells, which may be small capillaries (capillary haemangioma), large thin walled vessels (cavernous haemangioma, the most common type) or dysplastic malformation of arteries and veins (arteriovenous haemangioma or cirsoid aneurysm). Mixed forms are frequent. The prognosis of these tumours is unpredictable; they may even resolve (72,73), stop growing, or proliferate indefinitely. There is always the risk of recurrence, especially if there has been incomplete resection at initial surgery.

Localization

The most frequent locations are the lateral wall of the left ventricle (21%), the anterior wall of the right ventricle (21%), the interventricular septum (17%) and occasionally, the right ventricular outflow tract.

Figure 6.4 *Right atrial hemangioma in a 62-year-old woman with effort dyspnea. (a) Trans-oesophageal 2D echocardiography showing an atrial septal mass protruding into the atrial cavity to interfere with the blood flow: Color Doppler reveals an afferent coronary artery branch. (b) Selective coronary angiography confirms that the mass is vascularized from a collateral branch of the right coronary artery. (**c**) At histology, the mass consists of numerous vascular structures full of blood and lined by a single layer of endothelial cells (Heidenhain trichrome stain). (**d**) At immunohistochemistry, the lining cells are positive for endothelial markers (CD31). From Rizzoli G, et al., J Thorac Cardiovasc Surg., 2004.*



Macroscopy and histopathology

The tumours are often large and gross appearance depends on the size of the vascular spaces in the tumour. The capillary type is frequently slightly raised from the endocardial sruface and appears red to purple. Intramuscular types will appear infiltrative. Cavernous haemangiomas are usually large and are also poorly circumscribed. Capillary haemangiomas are composed of nodules of small capillary-size vessels, each of which is subserved by a “feeder” vessel. This lobular or grouped

arrangement of vessels is helpful for distinguishing these benign from malignant vascular proliferations. Mast cells and factor XIII-positive interstitial cells are a consistent feature. Intramuscular cardiac haemangioma has superficial resemblance to arteriovenous malformation, with the presence of heterogeneous vessel types, including muscularized arteries, veins, and capillaries. In contrast to capillary haemangioma, they are infiltrative lesions and occur within the myocardium.

Cavernous haemangiomas are composed of large dilated vascular spaces. They tend to infiltrate the myocardium. The lining cells are bland and flattened and mitotically inactive.

Genetic susceptibility

Genetic susceptibility to cardiac haemangiomas has not been identified. Extracardiac haemangiomas occur in a variety of contexts. They may be single sporadic lesions or multiple lesions that are components of complex genetic syndromes. Capillary haemangiomas occur in up to 10% of live births and are the most frequent tumour in newborns. When these tumours occur in the absence of associated syndromes, they may represent manifestations of an autosomal dominant mendelian trait. Linkage analyses of multiplex kindreds affected by hereditary capillary haemangiomas have identified loci on chromosome 5 (q31- q33 and q13-q22) that appear to contain as yet unidentified causal disease genes.

A wide array of complex syndromes, such as von Hippel Lindau syndrome and phocomelia/ Roberts syndrome, that can be transmitted in a mendelian fashion include haemangiomas as components of their clinical presentations. The Klippel-Trenaunay-Weber syndrome, in which cutaneous haemangiomas occur in the setting of osseous hypertrophy, shows familial clustering, but a clear mode of inheritance has not been established. Autosomal paradominant and dominant modes of inheritance have been proposed. Translocationshave been identified in 2 Klippel-Trenaunay-Weber patients, t(5;11) (q13.3;p15.1) and t(8;14)(q22.3; q13), but specific gene defects remain to be identified (2).

Somatic genetics

Specific genes have been associated with two disorders involving arteriovenous malformations. Mutations in the gene on chromosome 9p21 encoding the endothelial cell-specific receptor tyrosine kinase TIE2 cause the autosomal dominant Bean or "Blue rubber-bleb nevus" syndrome and familial multiple cutaneous and mucosal venous malformations. At least some cases of hereditary cerebral cavernous malformations are caused by mutations in the chromosome 7q21-q22 Krev interaction trapped-1, KRIT-1, gene KRIT1 normal binds to RAP1A, a Ras GTPase, and the disease causing mutations appear to disrupt these interactions. Other genetic loci for this disorder have been identified at chromosomes 17p15- p13 and 3q25.2-q27 and remain to be studied. The genetic and clinical relationship of this disorder to hereditary neurocutaneous angioma is unclear.

Syndromic associations

The majority of cardiac haemangiomas are sporadic and isolated, without evidence of extracardiac vascular lesions. Rarely, there may be extracardiac haemangiomas of the gastrointestinal tract and port-wine stain of the face. Giant cardiac haemangiomas can result in thrombosis and coagulopathies (Kasabach-Merritt syndrome) (2).

6.4 Lipoma

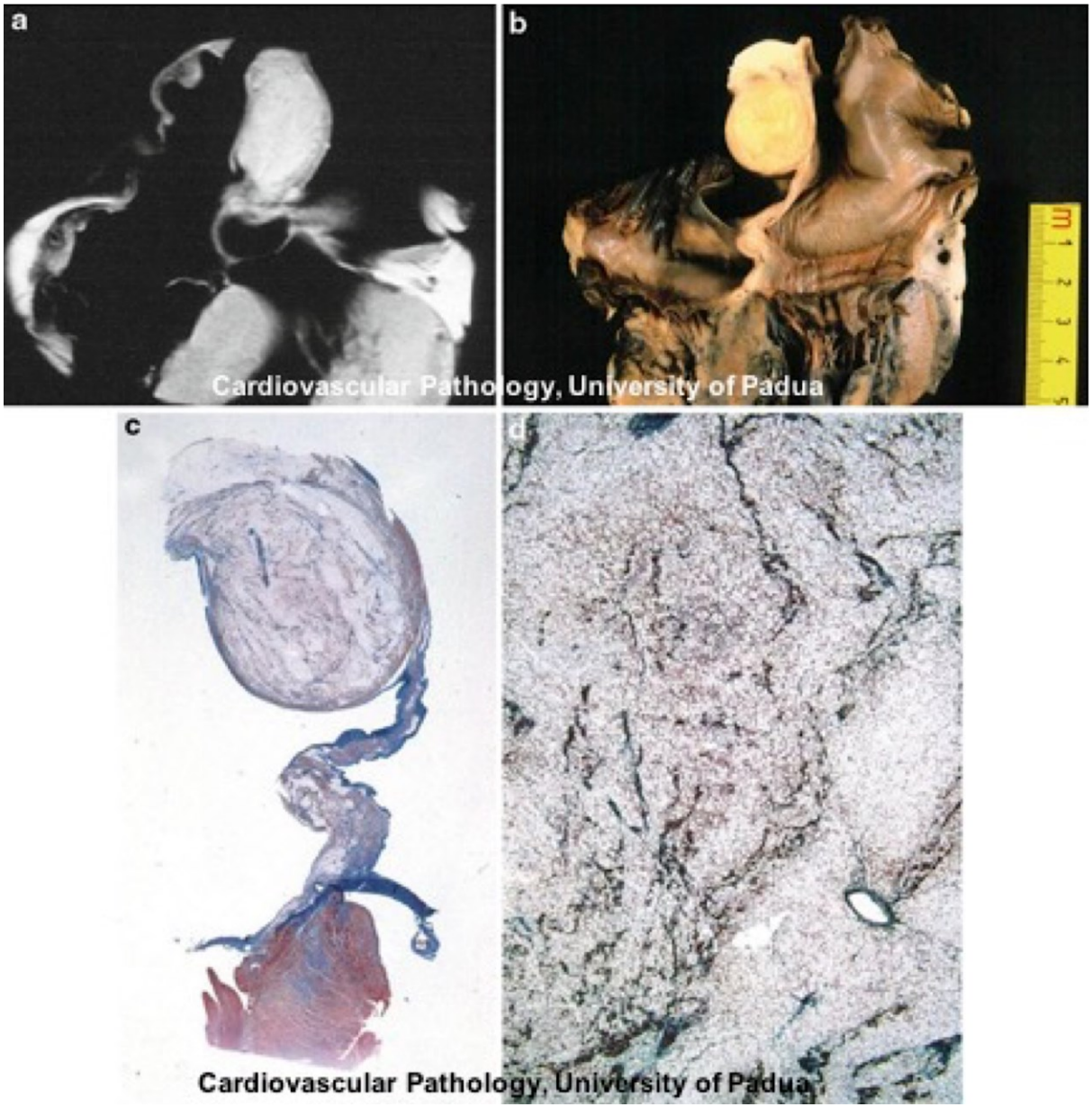
Definition: Benign tumour composed of mature, white adipocytes.

Lipoma was first described by Orth in 1886. It is a benign tumour made up of mature fat cells, reported at any age with equal frequency in both genders, with an incidence of 8% (1,2,75,76).

The true lipoma, which are single or multiple capsulated fatty masses, yellow, soft, and originating from the endocardium, epicardium or myocardium, should be kept distinct from so-called lipomatous hypertrophy of the interatrial septum. The latter, which should not be considered proper

by a tumour, is a non encapsulated adipose tissue mass, probably an intracardiac extension of the sub-epicardial fat of the right atrioventricular sulcus, usually observed in obese, old people (*Figure 6.5*) (77,78).

Figure 6.5 *Lipomatous hypertrophy of the atrial septum (atrial septal lipoma) at autopsy in a 74 year-old woman with a history of tuberculosis and diabetes (a) Ex vivo cardiac magnetic resonance showing a hyperintense signal similar to that of epicardial fat. (b) After longitudinal section of the heart, an oval-shaped lipomatous mass, 3x2 cm in size, is visible in the atrial septum. (c) At histology, the non-capsulated mass presents mature adipocytes with tiny interstitial fibrosis and rare cardiac myocytes (Heidenhain trichrome stain). (d) Close-up of C (Heidenhain trichrome stain). From Basso et al., Circulation, 1998.*



Localization

Cardiac lipomas may occur anywhere in the heart. There is a predilection for the pericardium and epicardial surfaces where they may attain enormous sizes. Other sites include the ventricular septum and cardiac valves. When they involve the latter site, the designation "fibrolipoma" has been used.

Histopathology

Similar to extracardiac lipomas, cardiac lipomas are circumscribed masses of mature adipocytes in a fine fibrovascular network, at difference from lipomatous hypertrophy which shows myocardial tissue with wide-spread infiltration of fat-cells (77,78).

Differential diagnosis

The main differential diagnosis is lipomatous hypertrophy, a non-encapsulated lesion composed of mature fat and adipocytes resembling brown fat cells intermixed with enlarged cardiac myocytes occurring solely in the interatrial septum. Lipomatous hypertrophy is most often an incidental finding at autopsy, but may uncommonly be the cause of unexplained atrial arrhythmias, AV Block, congestive heart failure, or superior vena cava obstruction.

The differential diagnosis also includes the intramuscular variant of haemangioma, which may contain variable numbers of adipocytes.

6.5 Fibroma

Fibroma is a rare primary heart tumour composed of fibroblasts or myofibroblasts with a matrix containing collagen. It almost exclusively occurs within the myocardium of the ventricles or ventricular septum. It is not clear whether it is a hamartoma or a true neoplasm. Because most cases occur in infants and children it is likely congenital. Fibroma is the second most common tumour in the paediatric population after rhabdomyoma (79-86). It represents nearly 20% of paediatric cardiac

tumours in Padua experience (1,6, 82,83).

Localization

Most fibromas are solitary, well circumscribed, firm, located within the left ventricular free wall or interventricular septum, thus producing compression of the conduction system, reentry ventricular arrhythmias or obstruction of the ventricular lumen (79,86). Atrial fibromas are quite rare.

Macroscopy and histopathology

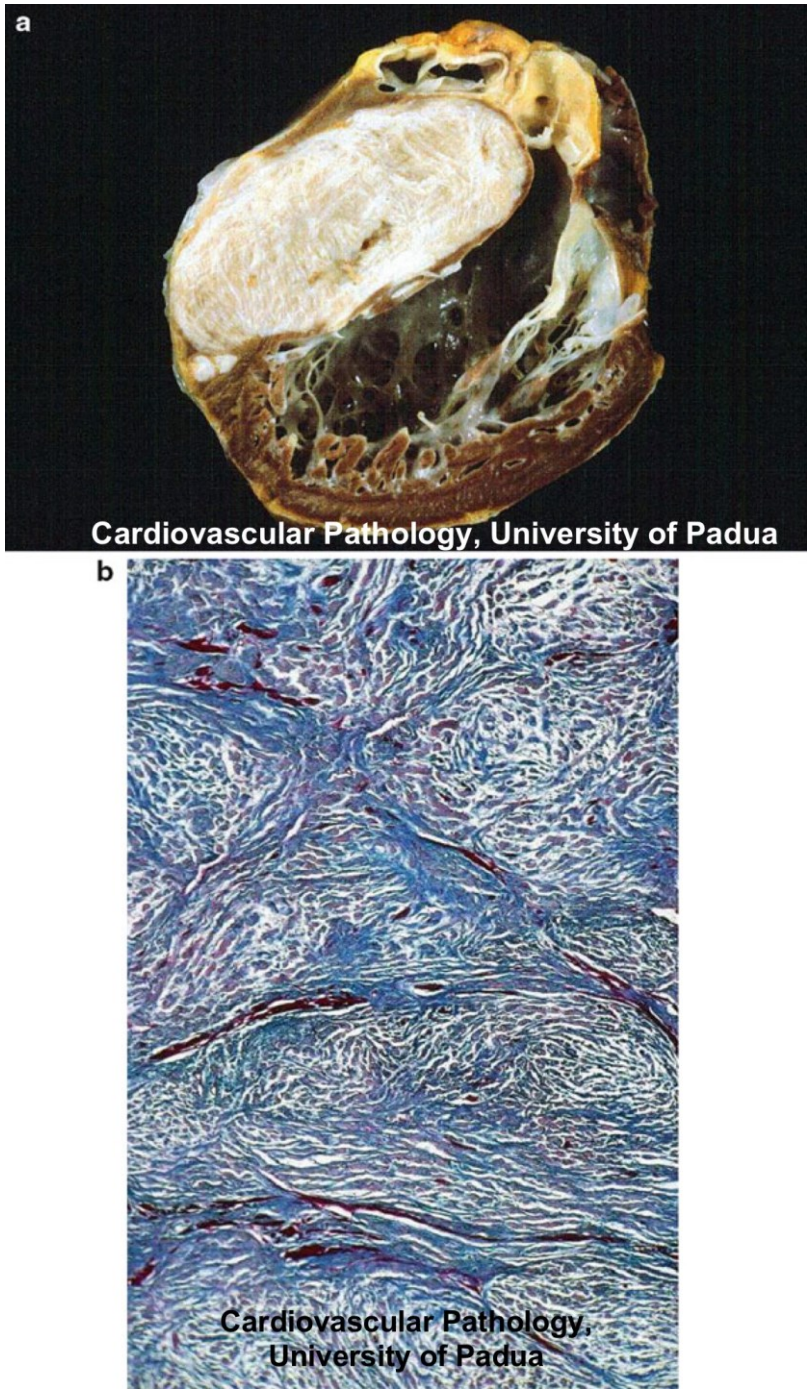
They are typically rounded masses that are fibrous, white and whorled. They are nearly always mural although polypoid endocardial based lesions have been reported. Most occur singly. The mean diameter is 5 cm. Fibromas are composed of bland-looking spindle cells forming loose intersecting bundles. They are not encapsulated and extend into the surrounding myocardium. Even in grossly circumscribed cases, entrapped myocytes can often be seen deep within the tumours, far from the gross margins. The fibroma cells have oval or tapered nuclei without nucleoli. Their cytoplasm is pale. These cells are associated with abundant collagenous stroma, which increases with the age of the patient. Tumour cells express vimentin and smooth muscle actin, both in cellular and fibrous lesions. Cellular lesions are observed in infants during their first months of life, while fibromas in older patients contain large amounts of collagen. Mitoses and foci of extramedullary haematopoiesis may be present in cellular tumours. Calcification is observed in lesions from patients of all ages, more common in older individuals. Wavy elastic fibers are frequent and may be prominent. Focal myxoid change in the stroma and chronic inflammation may also be present.

Prognosis and predictive factors

The cardiac fibroma is benign, but its nature of slow but continuous growth may cause conduction defects, arrhythmias with even sudden death. Extension into the ventricular free walls may result in atrioventricular valve inflow or arterial outflow obstruction. Spontaneous regression as can occur

with congenital rhabdomyoma has not been observed (*Figure 6.6*).

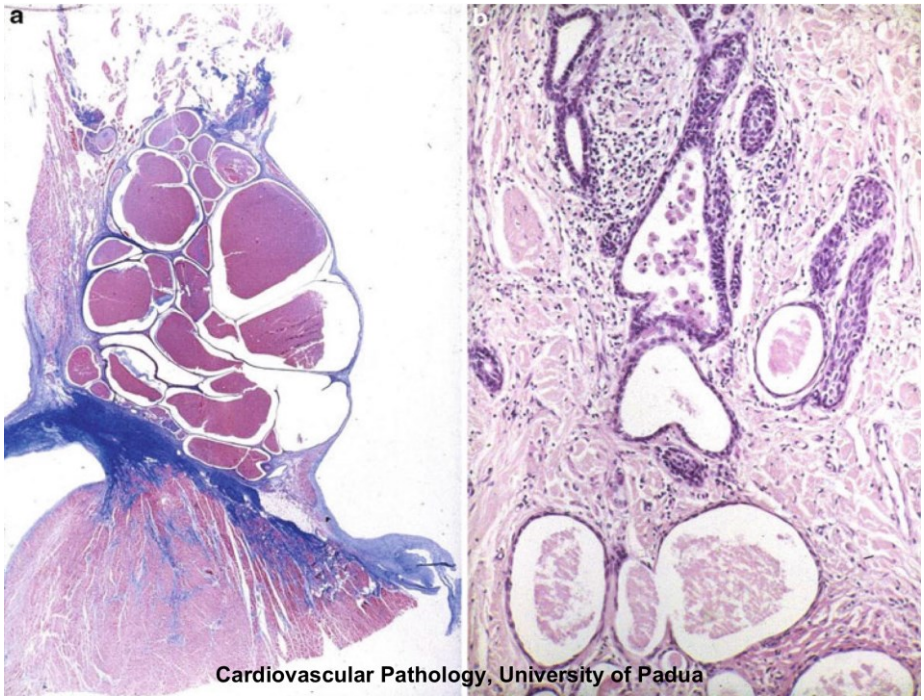
Figure 6.6 *A 40-year-old woman, with echocardiographic diagnosis of asymmetric hypertrophic cardiomyopathy, underwent cardiac transplantation due to refractorycongestive heart failure (a) Long axis section of the native heart showing a huge oval shape whitish mass occupying the interventricular septum and accounting for subaortic bulging/obstruction. (b) At histology, a cardiac fibroma was diagnosed (Heidenhain trichrome). From Valente et al., J Thorac Cardiovasc Surg, 1993.*



6.6 Cystic tumour of the atrioventricular (AV) node

The cystic tumour of the atrioventricular (AV) node, first described in 1911, involves the atrioventricular node selectively. It is also known as tawarioma (*Figure 6.7)*(from Tawara, who discovered the AV node) or celothelioma (mesothelioma of the AV node) reflecting its controversial histogenesis (87-91). The mean age of clinical presentation is nearly 40 years. The 75% of patients present with complete and 15% with incomplete AV block, whereas in 10% sudden death is the first clinical manifestation (92). On a large scale, the tumour appears multicystic, with size varying from 2 to 20 mm. Histologically, the tumour is located on the right side of the central fibrous body, infiltrating and compressing the AV node. The cysts are filled by a mucoid substance and are lined by epithelium, cytokeratin and epithelial membrane antigen positive (93). Diagnosis is usually achieved at post-mortem or after cardiac transplantation (94) through histological examination of the conduction system, but occasionally in vivo or during surgical resections.

Figure 6.7 *Cystic tumor of the AV node, incidental finding at autopsy in a 78-year-old woman who died of ischemic heart disease. Histologic section at the level of the AV node: note the subendocardial mass consisting of multiple cysts variable in size fi lled with mucoid material (Alcian PAS). (b) The cysts are lined by cuboid and transitional cells (hematoxylin–eosin stain. From Basso et al., Cardiac Tumor Pathology, 2013.*



6.7 Intracardiac blood cyst

Intracardiac blood cysts are rare, usually small and asymptomatic lesions, located in the endocardium most frequently along the closure rim of the atrio-ventricular valves in newborns and infants, particularly under 2 months of age, due to blood entrapped in the leaflet. The cysts are single blood-filled spaces lined by a layer of endothelial cells. They may regress spontaneously, thus are rare in adults. Occasionally, the blood sequestration may increase and the cyst assumes a huge endocavitary dimension, creates obstructive symptoms and requires surgery (95,96).

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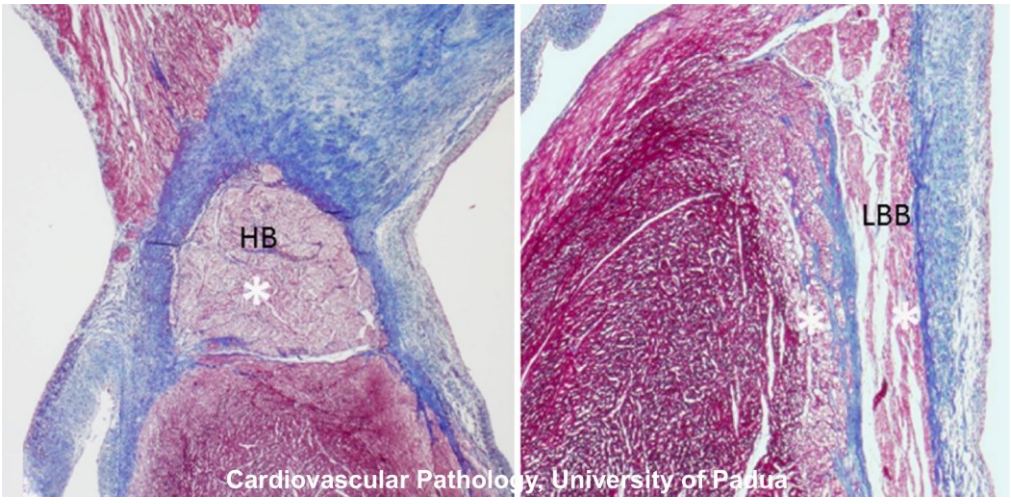
CHAPTER 7

OTHER CONGENITAL AND CHILDHOOD TUMORS

7.1 Histiocytoid Cardiomyopathy

Histiocytoid cardiomyopathy has in the past been designated oncocytic cardiomyopathy, Purkinje cell hamartoma, or cardiac hamartoma. It is a multifocal hamartomatous collection of cells that resemble modified myocytes of the conduction system (1). Histiocytoid cardiomyopathy is rare, with fewer than 150 reported instances (2) (*Figure 7.1*). Most affected patients are infants in the first year of life who have ventricular tachyarrhythmias or die suddenly. More than one-third of children have additional anomalies, both cardiac and extracardiac. Recently, a novel mutation in the NADH:ubiquinone oxidoreductase subunit B11gene (NDUFB11) has been identified in a few probands by direct sequencing, suggesting a role in the pathogenesis of the disease (3). There have been sporadic reports of mutations in mitochondrial genes; only a few cases (5%) are familial (4). Grossly, the tumors present as endocardial or myocardial nodules and may also involve the sinoatrial and atrioventricular nodes. Histologically, the cells are finely vacuolated, rounded myocytes that ultrastructurally demonstrate numerous mitochondria and disordered myofibrils.

Figure 7.1 *Histiocytoid cardiomyopathy. A serial histological sections study of the specialized conducting tissue reveals foci of histiocytoid cells (asterisks) in the His bundle (HB) and left bundle branch (LBB) as well as adjacent myocardium. From Rizzo et al., Heart Rhythm, 2014.*



7.2 Rhabdomyoma

Rhabdomyoma is considered the most common paediatric cardiac neoplasm, accounting for 90% of primary benign tumours in this age group (5-8). Nevertheless, in Padua surgical paediatric experience (9), only 15% of paediatric cardiac tumours were rhabdomyoma, since usually there is no indication for surgery because of spontaneous regression of the neoplasm along the natural history. Rhabdomyomas are single or, more frequently, multiple non-capsulated nodules, white or grey, up to 1–2 cm in diameter, usually intramural within the ventricular myocardium, but also intracavitary because of growth from the sub-endocardium (*Figure 7.2*).

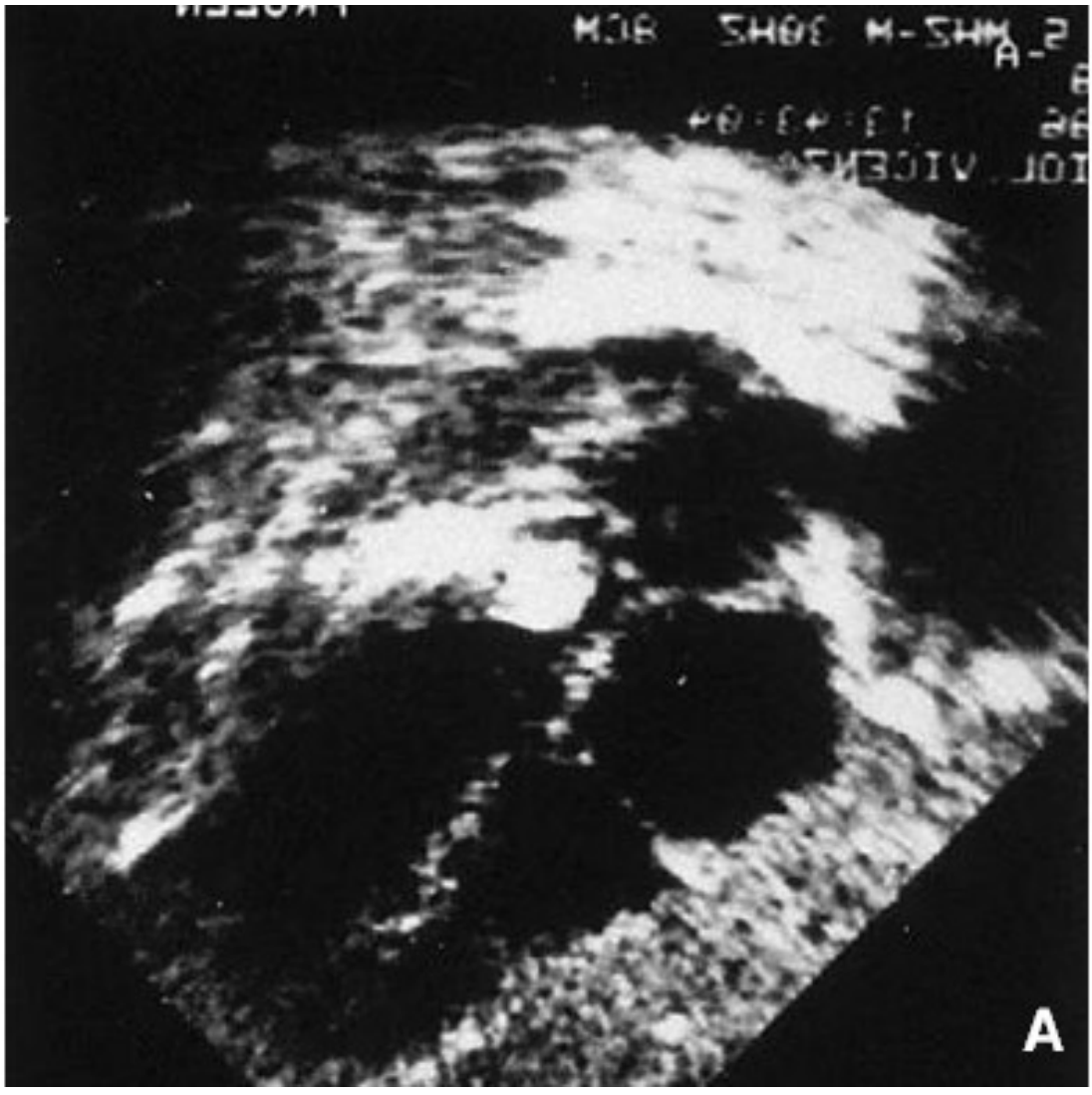
Rhabdomyomas are firm, white, well-circumscribed single or multiple lobulated nodules that occur in any location of the heart, but are more common in the ventricles (*Figure 7.3*). In patients with tuberous sclerosis, tumours are usually multiple (<90%) and can consist of numerous miliary nodules measuring less than 1 mm; in this instance, the term "rhabdomyomatosis" has been used and consisting of a classical clinical triad, i.e. neurofibromatous lesions, mental slowing and cutaneous lesions and due to mutation of genes coding for two tumour suppressors, amartin (9q34) and tuberin (16p 13.3). The most common locations are the left ventricle and ventricular septum, although 30% will have atrial wall or right ventricular involvement . In contrast to patients with tuberous sclerosis, approximately 50% of sporadic rhabdomyomas occur singly.

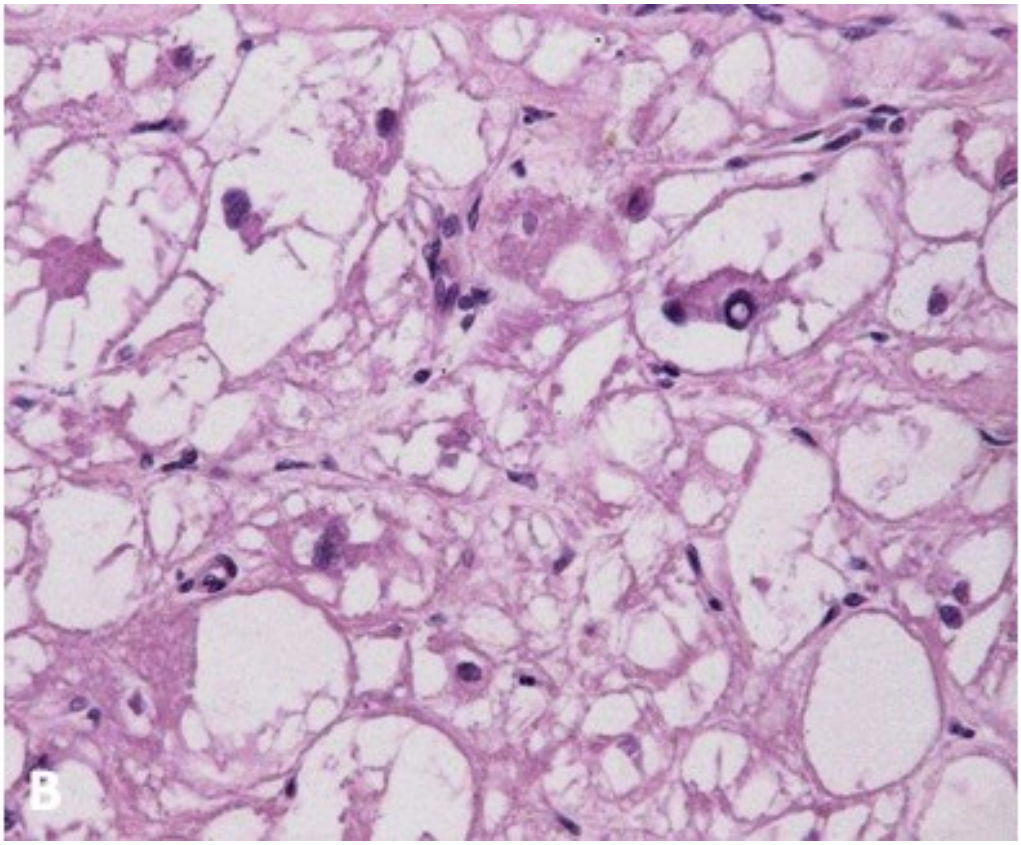
Single or multiple, they are well-circumscribed, non-capsulated white or grey white nodules which may vary in size from millimeters to several centimeters. Tumours can become quite large, especially in sporadic cases. They most often occur in the ventricle, but can be found in the atria, at the cavoatrial junction and on the epicardial surface. Large tumours may obliterate and distort a ventricular cavity.

Cardiac rhabdomyomas consist of large, vacuolated, clear myocytes full of glycogen, with residual cytoplasm stretching from the central nucleus to the membrane, giving rise to a spider appearance

("spider cells"). More than a proliferation of cardiomyocytes, the rhabdomyoma is a localised storage disease of glycogen, which may account for severe contractile ventricular dysfunction. The majority of cells show vacuolization with sparse myofilaments. There is a strong reaction with periodic acid-Schiff reagent, reflecting the presence of abundant intracellular glycogen (*Figure 7.2*) (10,11).

Figure 7.2 *Rhabdomyoma in a 7-month-old child with subaortic stenosis.* ***A*** *Two-dimensional echocardiography showing the left ventricular outflow obstruction due to an endocavitary mass attached to the anterolateral wall in the subaortic area.* ***B*** *At histology, patognomonic spider cells with cytoplasmatic myofibrils radiating to the cell periphery (hematoxylin-eosin stain). From De Dominicis et al, Chest. 1989;95:470–2.*

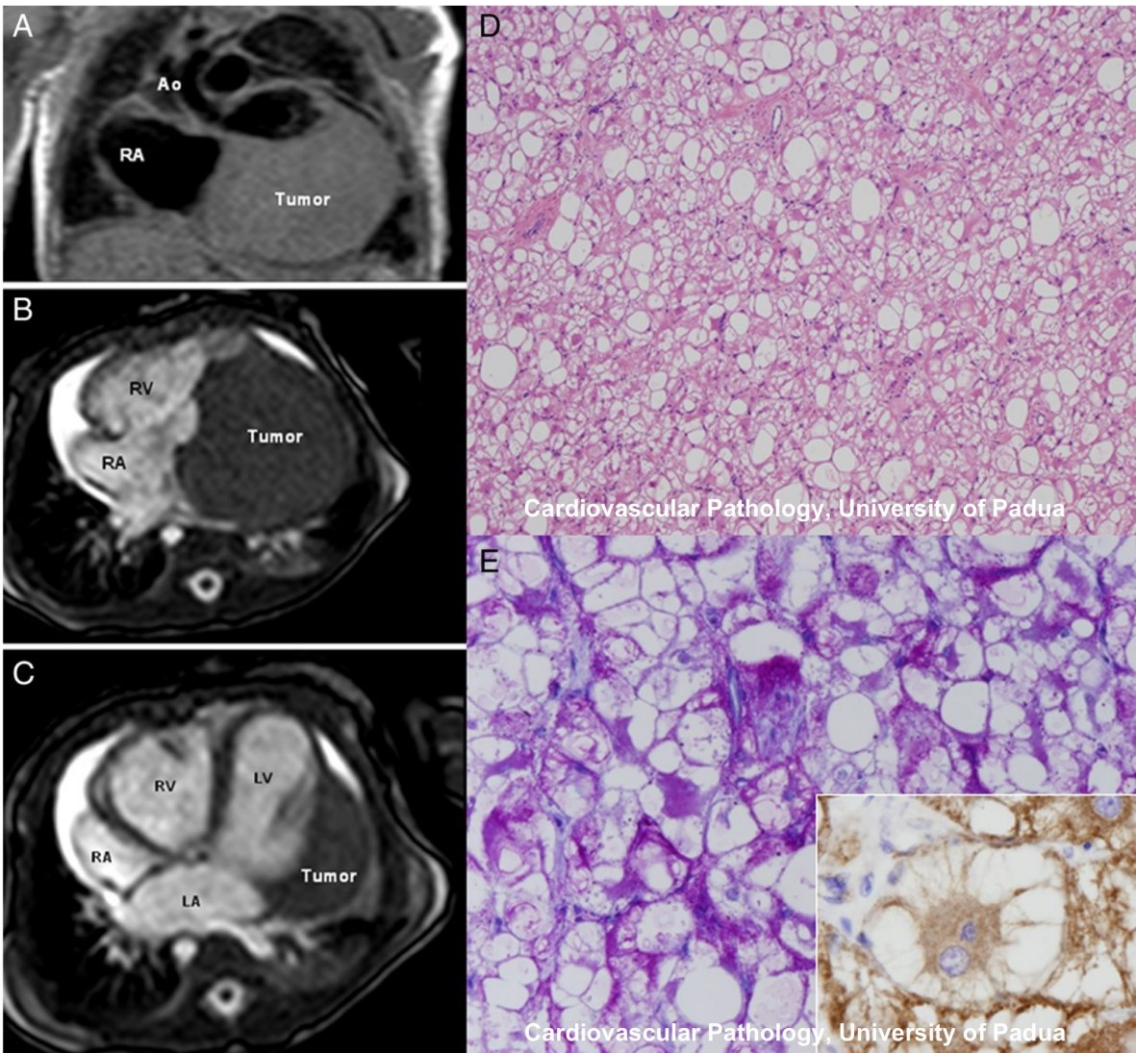




Immunohistochemical studies document the striated muscle characteristics of rhabdomyoma cells, which express myoglobin, desmin, actin, and vimentin. Tumour cells do not express cell proliferation markers such as Ki-67 and PCNA, indicating that the lesions are more likely hamartomas as opposed to neoplasms. The diagnosis of cardiac rhabdomyoma in infants and young children is straight-forward. Differently in the adult cellular rhabdomyoma there are striated myocytes and it is frequently similar to tumour of the head and the neck region (extracardiac rhabdomyoma). In contrast to congenital rhabdomyomas, adult cellular rhabdomyomas occur in adults, demonstrate evidence of cellular proliferation e.g. by expression of Ki-67 antigen, and contain relatively few vacuolated or spider cells. Unlike hamartoma of mature cardiac myocytes, the tumours are well circumscribed, and although not as frequent as in congential rhabdomyoma, some vacuolated cells are usually present. Furthermore, the disorganized masses of myofilaments characteristic of hamartoma of mature cardiac myocytes are not seen. Rhabdomyosarcoma shares some features with adult cellular rhabdomyoma. Despite the evidence of cell proliferation in the latter tumours, the absence of tumour necrosis, mitotic figures, myogenin expression, and the presence of a well-

defined pseudocapsule help to distinguish it from rhabdomyosarcoma. The prognosis of adult cellular rhabdomyoma is unknown, but presumed to be benign, based on the biologic behaviour of extracardiac rhabdomyomas in adults. Late recurrences have been described in extracardiac rhabdomyoma (1).

Figure 7.2 *CMR and histology features of intramural left ventricular mass. (A) ECG-triggered breath-hold proton density T1-weighted fast spin echo in coronal plane, showing a large homogeneous isointense mass involving the left ventricular wall; (B) ECG-triggered breath-hold cine steady-state free procession in axial plane, showing the cardiac mass involving the interventricular septum; (C) ECG-triggered breath-hold cine steady-state free procession in four-chamber view, showing no intracardiac obstruction; (D) Histopathology study shows enlarged swollen myocytes with clear cytoplasm and centrally located nucleus, connected with the periphery of the cell by strands of cytoplasm (spider cells); (E) the enlarged cells are vacuolated due to the abundant glycogen deposits in the cytoplasm; immunohistochemistry (inset) reveals striated muscular cell (spider cell) staining positive for myosin in keeping with cardiac rhabdomyoma. Ao, aorta; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle. From Padalino et al., Circulation, 2011*



7.3 Rare Hamartomas

"Hamartoma of mature cardiac myocytes," is composed entirely of heart muscle cells. Its distinction from rhabdomyoma is that the cells appear mature without the vacuolization seen in rhabdomyoma.

Unlike rhabdomyoma, hamartomas of mature cardiac myocytes occur in adults. Histologically, they resemble areas of myofiber disarray as seen in hypertrophic cardiomyopathy but are circumscribed masses.

Other rare hamartomatous tumors in the heart contain areas of mature fat as a component of the lesion. These include hamartoma of cardiac valves which have a mixture of fat and fibrous tissue, and rare intramuscular cardiac tumors with fat, vessels, heart muscle cells, and nerves. Because this so-called mesenchymal hamartoma has been reported only once and overlaps significantly with intramuscular hemangiomas (except for the nerve tissue), it is not considered a separate entity in the WHO classification of heart tumors (1).

7.4 Germ Cell Tumors (Teratoma and Yolk Sac Tumor)

Germ cells tumors are classified depending on the germ they derive from, such as seminoma (or dysgerminoma), embrional carcinoma, yolk sac tumor, choriocarcinoma, and teratoma (12). Diagnosis occurs typically within the first month of life (13,14). They are very rare, usually benign, in contrast with those occurring in adult age which are mostly malignant germ cell tumors. This is solitary, encapsulated cystic masses with intervening solid areas, often connected to the aortic root or to the pulmonary artery by means of a thin vascularized pedicle. They are usually localized at the base of the heart, anterior to the aorta, close to the superior vena cava, and may cause compression of these latter structures but also of the right atrium, atrial septum and ventricle and of the pulmonary artery (15). The neonate with an intrapericardial teratoma is usually severely

symptomatic Pericardial effusion is commonly associated. This may concur in causing a severe respiratory distress, cardiac tamponade, and low cardiac output syndrome that may be fatal if prompt diagnosis and treat- ment are not provided (16,17). Diagnosis is usually achieved with two-dimensional echocardiography during both the fetal and the neonatal period (15,16).

Surgical resection of the mass is often lifesaving (18).

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CHAPTER 8

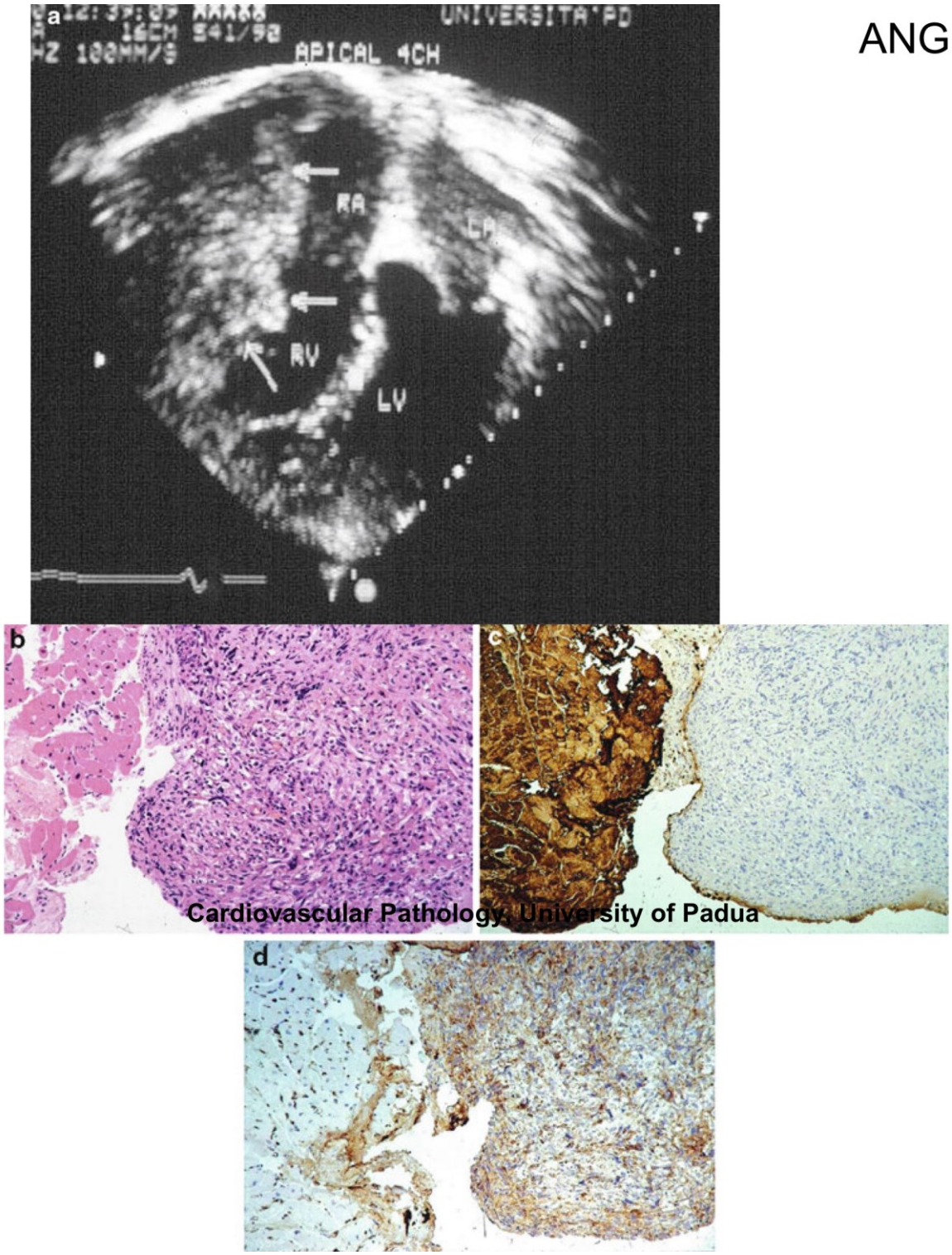
PRIMARY MALIGNANT CARDIAC TUMOURS

Primary malignant cardiac tumours are very rare, representing nearly 10% of all primary cardiac neoplasms (1,2). Sarcomas represent 95% of these tumours (about 10% of all primary cardiac tumours, angiosarcomas and unclassified sarcomas being the most common accounting for 76%), and primary lymphomas and mesotheliomas make up the remaining 5% (3-11). All varieties of soft tissue sarcomas have been reported to arise in the heart. Primary cardiac sarcomas can occur at any age, but are more frequently diagnosed between the third and fifth decades, and equally in men and women (2), whereas they are extremely rare in the paediatric age group. Surgical excision is the most effective treatment for primary cardiac malignancies. However, prognosis is very poor in spite of additional treatments, such as radiotherapy and chemotherapy, with a median survival of less than one year and 80% of patients already present diffuse infiltration of the heart and metastases at the time of diagnosis (8-12). A less-aggressive course seems related to the left atrium location, a low histologic grading with scarce cellular pleomorphism and low-mitotic activity, absence of necrosis, and absence of metastasis at diagnosis.

8.1 Angiosarcoma

Angiosarcoma is the most common primary malignant cardiac tumour, with a peak in the 4th decade and no sex predilection (1,2,12). The most frequent location is the right atrial chamber. The presenting signs and symptoms are non-specific and may include right sided heart failure, symptoms of pericardial involvement or vena cava obstruction. Echocardiography usually demonstrates a broad based right atrial mass near the inferior vena cava and AV sulcus. On CT and MRI they show arterial phase enhancement permitting a definitive diagnosis.

Figure 8.1 *Angiosarcoma in 36- year-old woman, suffering from dyspnea and fever (a) Two-dimensional echocardiogram, apical four-chamber view, showing an irregular, both endocavitary and intramural large mass (arrows) in the right atrium (RA), extending into the right ventricle (RV), 6x8cm in size. (b) Histology of the transvenous endomyocardial biopsy of the mass: the myocardium appears infiltrated by pleomorphic spindle cells with hyperchromatic nuclei forming vascular channels (hematoxylin–eosin stain). (c) Immunostaining against myoglobin is strongly positive in the normal myocardium but not in the neoplastic proliferation. (d) The tumor cells arranged in vascular channels are positive to factor VIII (LV left ventricle)*
From Poletti et al., Cardiovasc Pathol., 1993.

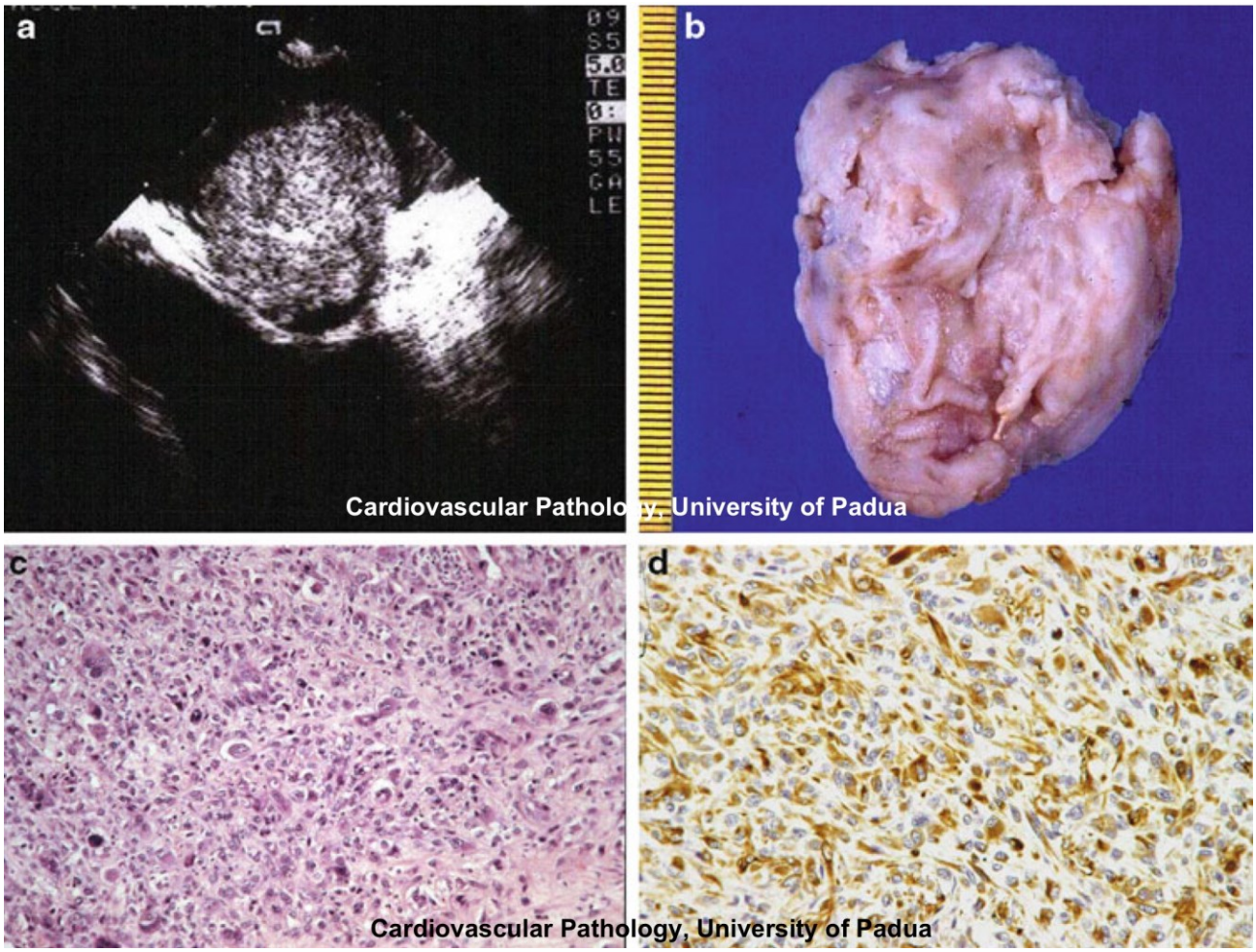


Pulmonary metastases are frequent, and survival after diagnosis rarely exceeds 6 months. On a large scale, it is an intramural neoplasm, brownish and lobulated, infiltrating the wall and the pericardium, and protruding into right cardiac cavities, with invasion of the inferior vena cava and the tricuspid orifice. The site is ideal for in vivo diagnosis through endomyocardial biopsy (13). At histology, two thirds of angiosarcoma are well to moderately differentiated and show an irregular, anastomosing, vascular network, lined by pleomorphic, atypical cells with frequent mitoses. In one third of cases, the tumour is poorly differentiated, consisting of anaplastic spindle cells within a hyaline stroma, containing focally extravascular red cells. Immunohistochemistry plays a crucial role in diagnosis, confirming the endothelial nature of malignant cells, strongly positive with factor VIII, CD31 and CD34 *(Figure 8.1).*

8.2 Malignant pleomorphic fibrous histiocytoma (MFH)/undifferentiated pleomorphic sarcoma

Malignant pleomorphic fibrous histiocytoma (MFH)/undifferentiated pleomorphic sarcoma accounts for one-third of all cardiac sarcomas and have been incorporated in the malignant fibrous histiocytoma/pleomorphic sarcoma subgroup (1,2).

Figure 8.2 *Left atrial malignant fibrous histiocytoma in a 68 -year-old man, presenting with fever and increased serum in fl ammatory markers. (a) Two-dimensionalechocardiography: an endoluminal round mass is visible in the left atrium, simulating a myxoma. (b) Grossly, the surgical resected mass showed a rough and irregular surface. (c) At histology, bizarre cells with pleomorphic nuclei admixed to giant cells and spindle-shaped cells, with high mitotic rate are seen (hematoxylin–eosin stain). (d) At immunohistochemistry, the tumor cells are positive to vimentin. From Basso et al., Cardiac Tumor Pathology, 2013.*



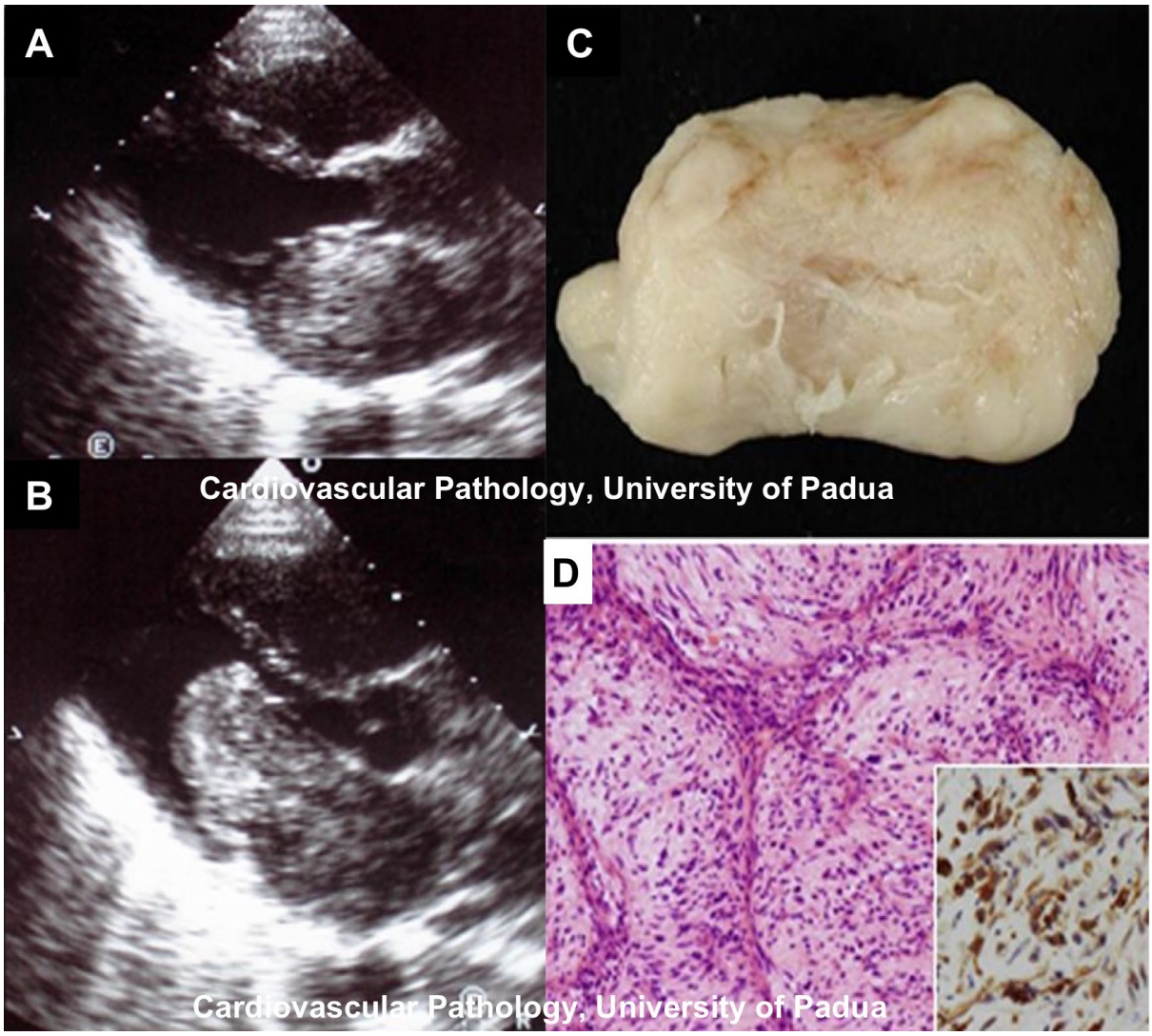
This is an exclusion diagnosis, when all the immunohistochemical stains fail to give evidence of specific differentiation. Once, when immunohistochemistry was not available, undifferentiated sarcoma represented 50% of all cardiac malignancies, but in more recently published series it has almost disappeared. Most frequently it arises in the left atrium, with an endocavitary growth, mimicking left atrial myxoma at echocardiographic examination. Differential diagnosis should also consider intracavitary thrombi. Macroscopically, the mass is clearly distinguishable from myxoma because it may be multiple, whitish with a rough surface and hard consistency, in the absence of gelatinous appearance. Microscopically, it consists of pleomorphic cells, frequently giant multinuclear, with high mitotic activity and positivity only for vimentin at immunostaining *(Figure 8.2).*

8.3 Leiomyosarcoma

Leiomyosarcoma is a primary sarcoma of smooth muscle cells and accounts for nearly 10% of all cardiac malignancies, with a peak in the 5th decade and no sex prevalence (1,2,14,15).

There are two usual sites of origin. One is the left atrium, where it may present as a single or multiple endocavitary mass, mimicking the left atrial myxoma although usually attached to the atrial roof rather than the atrial septum (14); the second, is the pulmonary infundibulum and artery, mimicking pulmonary embolism (15). On a large scale, the mass is irregular, solid, and whitish or grey. Histologically, fascicles of spindle cells, smooth muscle actin and desmin positive, with blunt-ended nuclei, oriented at right angle with mitoses are visible. Pleomorphism, giant cells and necrosis are focally present *(Figure 8.3).*

Figure 8.3 *Left atrial endocavitary mass. (A and B) Two-dimensional echocardiography, parasternal long-axis view (systole and diastole): note the tumour prolapse during diastole and the mass attached to the roof of the left atrium; (C) Gross examination of the surgically resected mass: note the firm, homogeneous and whitish appearance; (D) Histology shows pleomorphic cells arranged in a storiform pattern with a myxoid background; the cells are staining positively for desmin (inset), in keeping with a diagnosis of leiomyosarcoma. From Basso et al., Heart, 2016.*



8.4 Fibrosarcoma

Fibrosarcoma consists of a malignant proliferation of mesenchymal cells with fibroblastic features and a storiform, herring-bone pattern with a collagen stroma (1,2,16) (*Figure 8.4*). They represent nearly 5% of all primary cardiac malignancies. The most frequent location is in the atria (particularly the left), with both intracavitary and mural location. A pericardial form does exist

(solitary malignant fibrous tumour of the pericardium), which may mimic a mesothelioma. As with other sarcomas, clinical presentation depends on the site and size of the tumour. Being mostly left sided, signs and symptoms of pulmonary congestion, mitral stenosis and pulmonary vein obstruction are the most frequent.

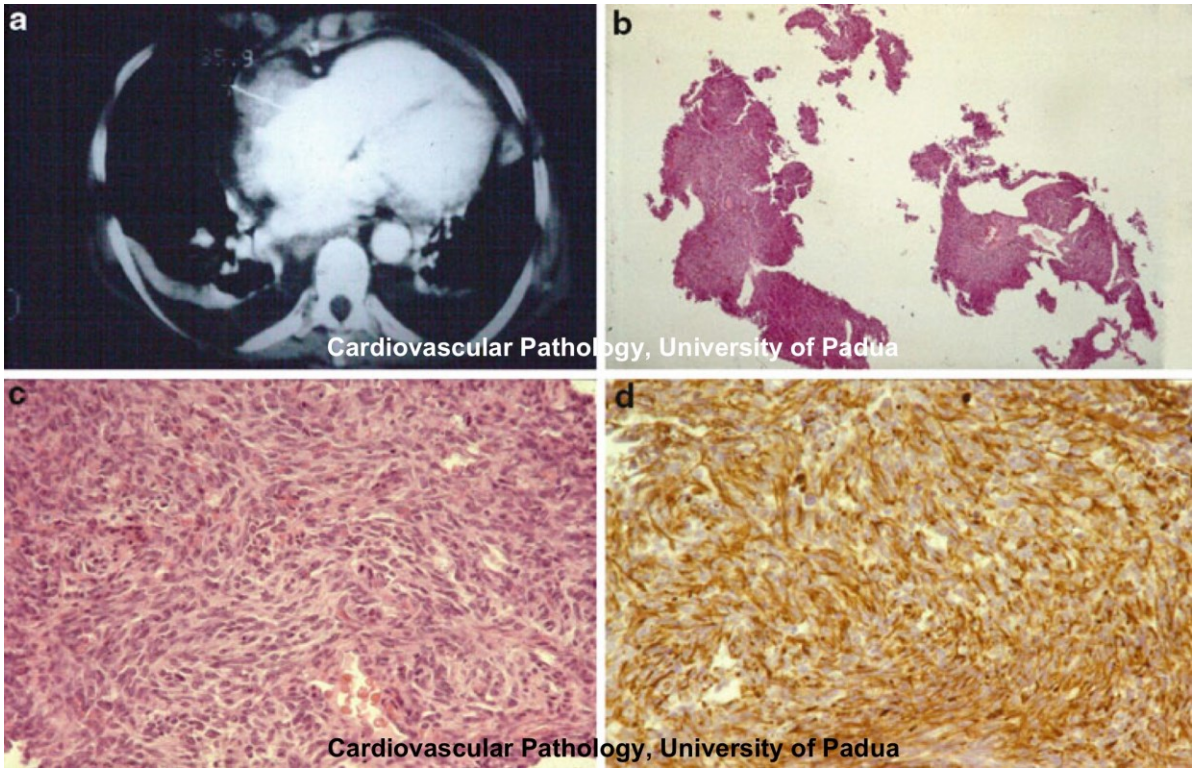
Microscopically, the fibrosarcoma consists of a collagen stroma and monomorphic spindle cells, with variable mitotic index. Pleomorphism, giant cells and vascularisation are absent.

Immunohistochemistry is positive for vimentin and frequently also for actin, in keeping with a myofibroblastic differentiation.

The prognosis is poor (mean survival 5 months), even in intracavitary cases in which surgical resection is apparently radical.

Myxoid fibrosarcoma is grouped among fibroblastic/ myofibroblastic neoplasms.

Figure 8.4 *Fibrosarcoma of the right atrium in a 62 -year-old woman, suffering from weakness and effort dyspnea. (a) CT showing a mass in fi ltrating the right atrial free wall. (b) Transvenous endomyocardial biopsy: panoramic view of bioptic specimens (hematoxylin–eosin stain). (c) At higher magni fi cation, note atypical spindle cells within a fi brous stroma (hematoxylin–eosin stain).(d) At immunohistochemistry, the tumor cells are positive for vimentin. From Basso et al., Cardiac Tumor Pathology, 2013.*

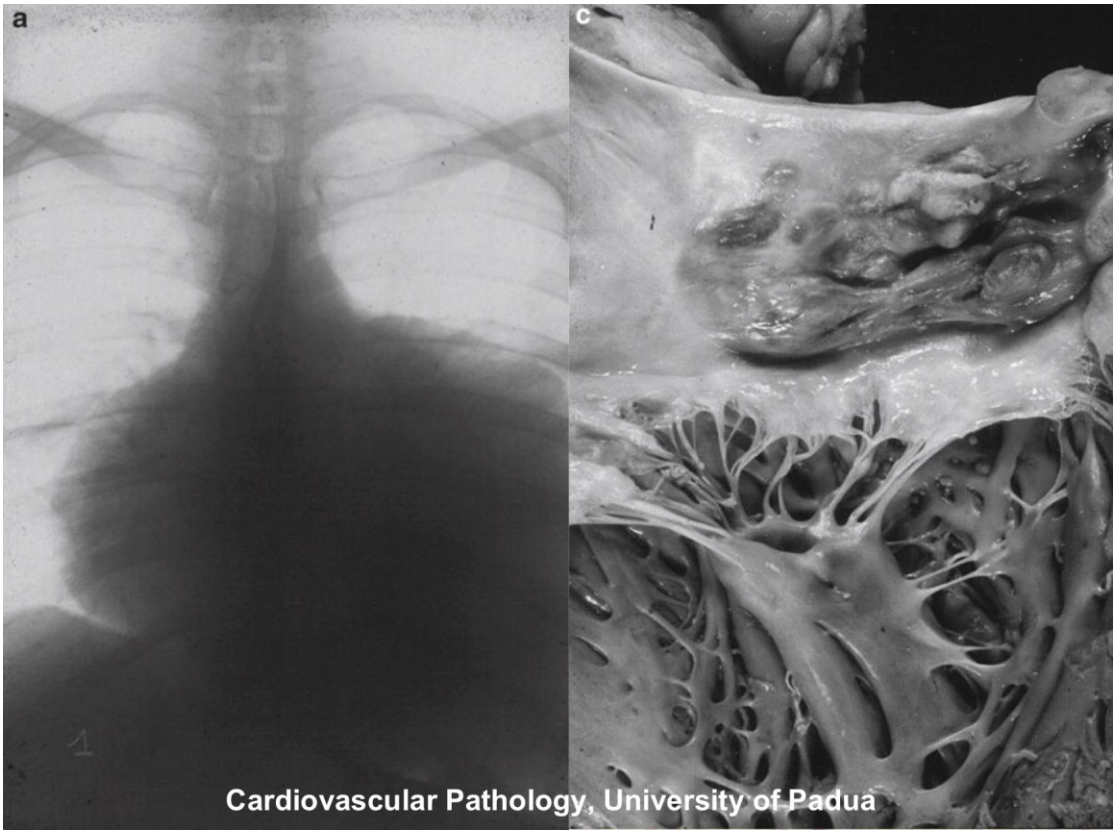


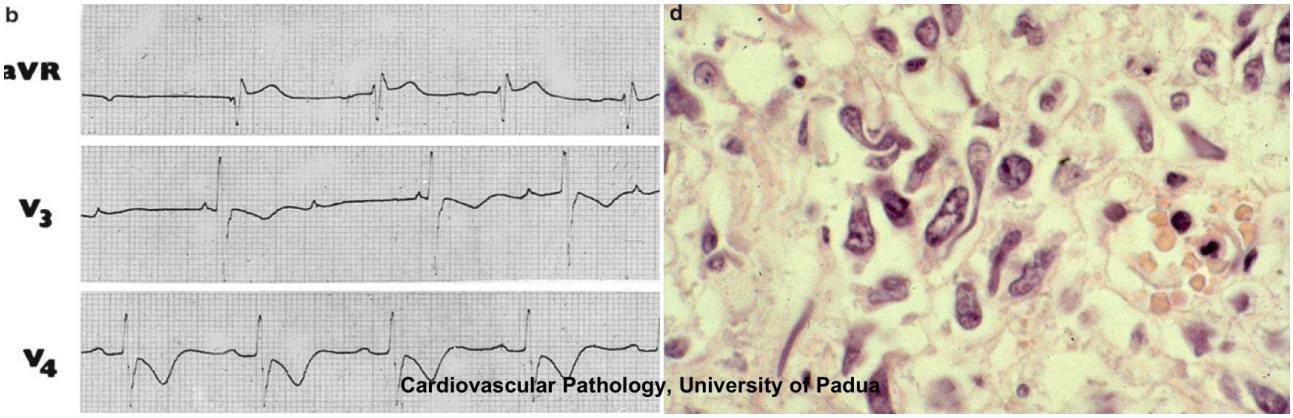
8.5 Rhabdomyosarcoma

Rhabdomyosarcoma is a rare malignant tumour of striated muscle, most frequently encountered in children with male prevalence (1,2,17) (*Figure 8.5*). Rhabdomyosarcomas arise de novo, not from malignant degeneration of a rhabdomyoma. It often diffusely infiltrates the myocardium at any location, presenting with cardiac obstructive phenomenon, arrhythmias or pericardial effusion.

Embryonal rhabdomyosarcoma is the most frequent at cardiac level thus explaining the younger age at presentation. Within a rich proliferation of round cells with frequent mitoses, PAS positive rhabdomyoblasts are visible with the typical feature of "tadpole" and positive at immunohistochemistry for vimentin, muscle-specific actin, desmin and myogenin. Electron microscopy reveals cells containing contractile filaments with a "Z-band-like" appearance.

Figure 8.5 *Rhabdomyosarcoma in a 36- year-old patient at autopsy. (a) Chest X-ray shows pericardial and right pleural effusion. (b) At ECG, atrio-ventricular dissociation is present. (c) At autopsy, the tumor appears as a bulky mass in fi ltrating the left atrial posterior wall. (d) At histology, tumor cells appear pleomorphic and tadpole-like, with small transverse bands in the cytoplasm (hematoxylin–eosin stain. From Basso et al., Cardiac Tumor Pathology, 2013.*





8.6 Liposarcoma

Liposarcoma is a rare entity (1% of primary malignant tumours of the heart) (1,2) that predominantly appears as a bulky endocavitary left atrial mass, mimicking myxoma, with early signs of local invasion and haemodynamic disturbance.

It looks like an intramural, sessile or pedunculated mass, gelatinous and un-encapsulated. Microscopically, it consists of lipoblasts, irregular cells, with large pleomorphic nuclei and cytoplasmatic fat vacuoles, S100 positive at immunohistochemistry.

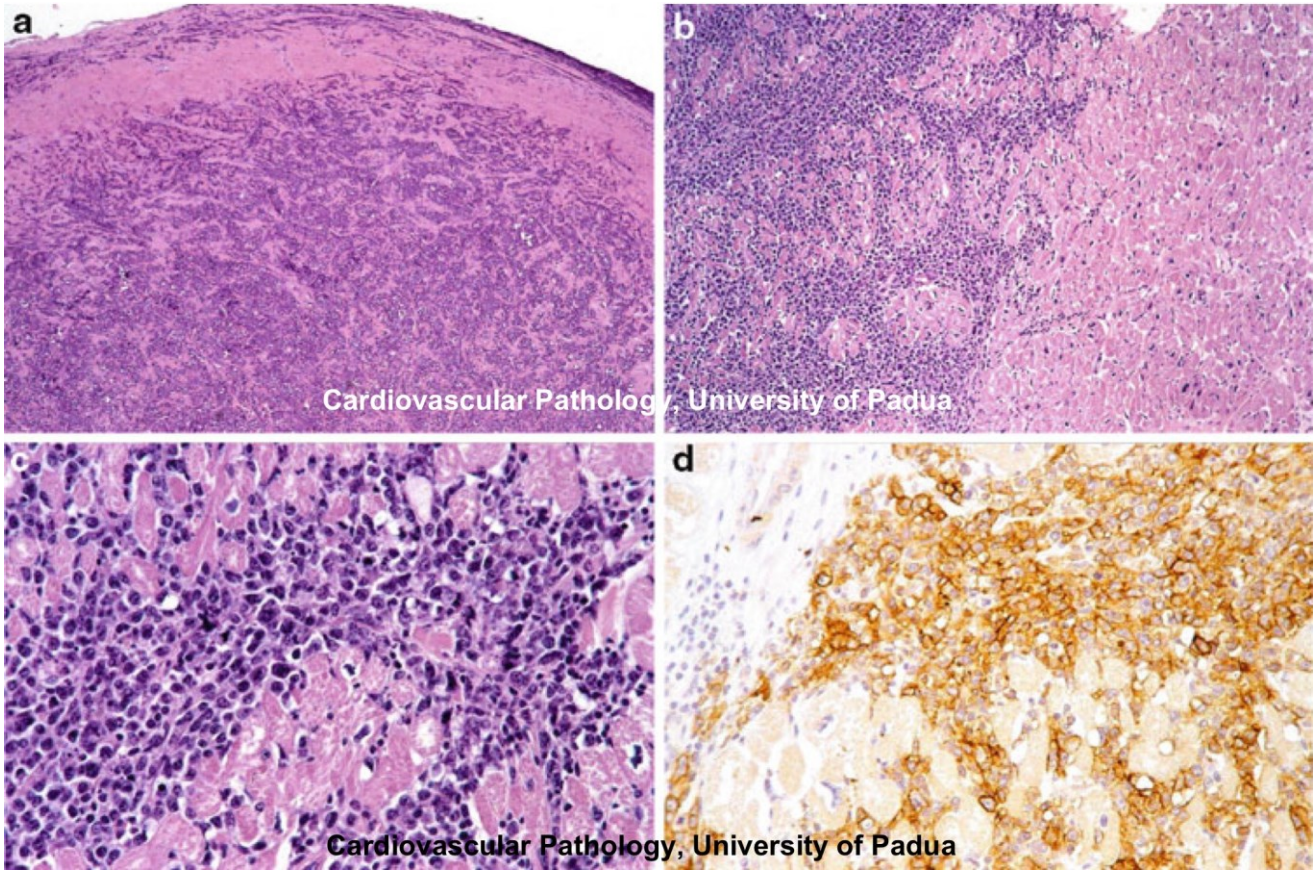
8.7 Cardiac lymphoma

It represents 5% of primary cardiac malignant neoplasms, which means 1% of all cardiac primary tumours. It occurs in ages from 5 to 90 years (median 60), the male/female ratio is approximately 3:1, and it does not necessarily occur in immune-deficient people. It ay arise in any cardiac chamber, but in 2/3 of cases the right atrium is the site of involvement with an intramural, whitish infiltrating mass extended to pericardium with massive effusion.

Primary cardiac lymphoma is an extranodal non-Hodgkin's lymphoma. The subtype most frequently observed (80% of cases) is B-cell lymphoma with huge, CD20 positive cells, whereas the

remaining 20% are CD3 positive T-cell lymphomas. Cytology of pericardial effusion may be of help for diagnosis, by using molecular techniques to differentiate B and T-cell lymphomas from reactive lymphocyte hyperplasia. Primary cardiac lymphomas should be promptly treated like aggressive lymphomas in other sites, since a late diagnosis is the major determinant of a poor prognosis. It is worthwhile to note that primary cardiac lymphomas, with chemo-therapy, are the only malignant cardiac neoplasms to present a fairly good prognosis (1,2)(*Figure 8.6*).

Figure 8.6 *Primary cardiac lymphoma in a 36- year-old man, drug abuser and HIV infected, with echocardiographic finding of a mass infiltrating the right atrial free wall. (a) The myocardium is diffusely infiltrated by proliferating neoplastic cells (hematoxylin–eosin stain).(b) Border area between the neoplastic in filtration and normal myocardium (hematoxylin–eosin stain). (c) At higher magnification, the tumor cells are large with large nuclei (hematoxylin–eosin stain). (d) At immunohistohemistry, tumor cells are positive for CD20, a B-cell marker. From Basso et al., Cardiac Tumor Pathology, 2013.*



8.8 Grading

For many years, no universally accepted classification of primary cardiac sarcomas existed. The difficulty derived from the rarity of cardiac sarcomas reported in the literature. All soft tissue sarcoma types have also been found to arise in the heart. There is no grading system for malignant cardiac tumors and criteria for soft tissue neoplasms are used (18). As for soft tissue, cardiac sarcomas can be classified by biological and histologic aspects.

First, in the new WHO classification of Soft Tissue Tumours it is recommended to divide soft tissue tumours into the following four categories: benign, intermediate (locally aggressive), intermediate (rarely metastasizing) and malignant (18).

Second, histologic grading of malignancy of cardiac sarcomas has the greatest correlation with survival, with the important exception of angiosarcoma.

Grading, based on histological parameters only, evaluates the degree of malignancy and mainly the probability of distant metastasis. Staging, based on both clinical and histological parameters, provides information on the extent of the tumour. The concept of grading in soft tissue tumors was first properly introduced by Russell et al in 1977 (19), and was the most important factor of their clinico-pathological classification. Several grading systems, based on various histological parameters, have been published and proved to correlate with prognosis (20-23). The main parameters in non-cardiac soft tissue tumors are the mitotic index and the extent of tumor necrosis (18,20). Three grades of malignancy are usually identified: G1, low grade; G2, intermediate grade; G3, high grade. The French Federation Nationale des Centres de Lutte Contre le Cancer (FNCLCC) classification is the grading system that seems to better correlate with survival of soft tissue sarcomas. The FNCLCC system is based on a score obtained by evaluating three features: tumor differentiation, mitotic rate, and amount of tumor necrosis. A score is attributed independently to each of the three parameters and the final histological grade is the sum of the three attributed scores (*Table 8.1*) (21).

Table 8.1 *Parameters of the grading system for sarcomas of the Féderation Nationale des Centres de Lutte contre le Cancer (FNCLCC) Modified from Trojani et al. Int J Cancer. 1984.*

Tumor differentiation	
Score 1	Sarcomas closely resembling normal adult mesenchymal tissue (e.g., low-grade leiomyosarcoma)
Score 2	Sarcomas for which histological typing is certain (e.g., myxoid fibrosarcoma)
Score 3	Undifferentiated sarcoma, angiosarcoma
Mitotic count	
Score 1	0–9 mitoses per 10 HPF[a]
Score 2	10–19 mitoses per 10 HPF[a]
Score 3	≥20 mitoses per 10 HPF[a]
Tumor necrosis	
Score 0	No necrosis
Score 1	<50% tumor necrosis
Score 2	≥50% tumor necrosis
Histological grade	
Grade 1 (G1)	Total score 2, 3
Grade 2 (G2)	Total score 4, 5
Grade 3 (G3)	Total score 6, 7, 8

[a] A hight-power field (HPF) measures 0.1734 mm^2

As a general rule, grading should be used only for untreated primary soft tissue sarcomas and should be performed on representative material (for instance, tissue obtained through endomyocardial biopsy cannot be used for grading purposes).

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CHAPTER 9

TUMOURS OF THE PERICARDIUM

Primary pericardial tumours are rare, and include benign (cyst, teratoma, fibroma, angioma and lipoma) and malignant (mesothelioma and sarcoma) forms. More frequently, the pericardium is secondarily involved by direct extension, retrograde lymphangitic spread or hematogenous dissemination. The patients present with pericardial effusion and occasionally pericardial tamponade (1,2).

9.1 Pericardial cyst

A pericardial cyst is a relatively frequent mass, uni- or multiloculated, full of serous liquid, probably disontogenetic in origin, but symptomatic in adult age because of increasing storage of fluid within the cystic cavity. Histologically, the thin wall consists of highly vascularised connective tissue covered by mesothelium on both sides (3).

9.2 Teratoma

Teratoma is a tumour of germinal cells, which represents nearly 10% of all paediatric cardiac tumours. In 90% of cases it is located within the pericardial cavity, usually at the base of the heart. Diagnosis is usually achieved within one month of age because of severe obstructive symptoms by compression of the arterial pole. Pericardial effusion may occur and lead to cardiac tamponade. On a large scale, they appear as cystic lesions, clearly visible with clinical imaging. Histologically, proliferation of various tissues from two or three embryonic leaflets is visible (gastrointestinal, cartilagineous, bony, bronchial, nervous), easily identified by immunohistochemistry (3).

9.3 Malignant Mesothelioma

Malignant mesothelioma is the most common primary malignancy of the pericardium. It accounts for only about 1% of all mesotheliomas. It affects individuals of any age (mean 45 years), with a male predominance. The role of asbestos in pericardial mesothelioma is unclear. A role for radiotherapy for mediastinal neoplasms and breast cancer has also been advocated (4). Mesothelioma arises from the mesothelium. It occurs most frequently as diffuse pericardial thickening, encasing the heart. The cells are large pleomorphic cells with abundant pale cytoplasm and well demarcated cell borders, positive for cytokeratin, vimentin, epithelial membrane antigen and calretinin and negative to carcinoembryonic antigen, the latter being instead positive in pericardial metastasis of adenocarcinoma. It is in fact imperative to rule out any neoplasm with secondary pericardial involvement (4).

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CHAPTER 10

METASTATIC TUMOURS TO THE HEART

Definition

The heart can be the target of metastases from any extracardiac malignant neoplasm able to spread to distant site. Metastatic tumours are malignant cardiac neoplasm that may be infiltrate the myocardium and may be frequently associated with pericardial metastases, especially in the cases of carcinomas, which additionally involve mediastinal lymph nodes.

Epidemiology

The incidence of secondary cardiac tumors at autopsy ranges from 1.7% to 14% (average, 7.1%) in cancer patients and from 0.7% to 3.5% (average, 2.3%) in the general population (1). In contrast to older series, a significant increase in the incidence of cardiac metastases in cancer patients was noted after 1970, predominately because of improvement in imaging modalities. An investigation performed at Padua University in the time interval 1967-1976 revealed that among 7,460 autopsies the cause of death was malignancies in 1,181 cases (15,33%), in 74 of which cardiac metastases occurred (2).

Clinical features

The cardiac location of the tumor greatly affects the signs and symptoms. These can include symptoms related pericardial effusions, arrhythmias, or congestive heart failure. Obstruction of the mitral or aortic valve may cause syncope. Involvement of the right heart and tricuspid valves may give rise to right-sided failure. The symptoms of cardiac metastases are extremely variable and depend on the location of the tumor. Dyspnea, palpitations, syncope, chest pain, and peripheral

edema are common clinical findings (3,4).

Localization

Cardiac metastases can occur either by direct extension, via the bloodstream or lymphatics, or by intracavitary diffusion through the inferior vena cava (IVC). Pericardial metastasis (69%) is the most common, followed by epicardial (34%), myocardial (32%), and endocardial metastases (5%) (3). The pericardium is most often involved because of direct invasion by thoracic cancer, including breast and lung cancer (*Figure 10.1)*.

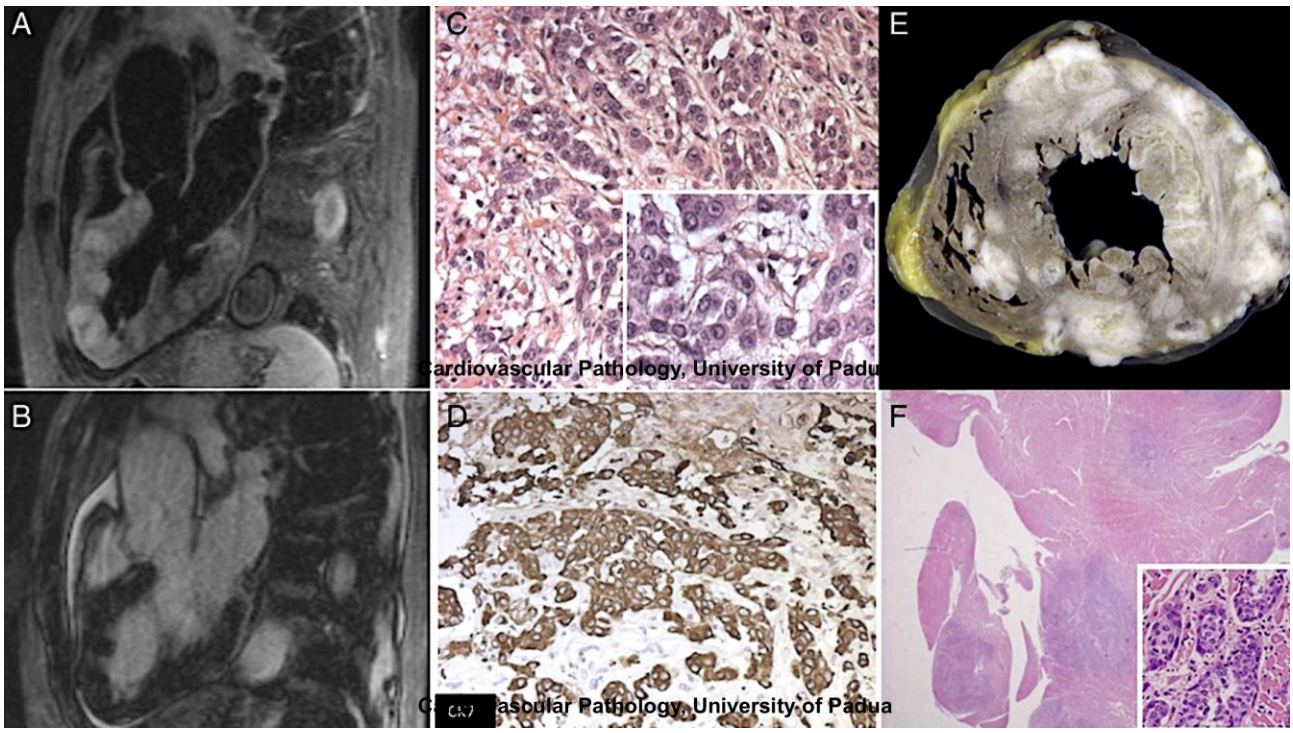

Figure 10.1 *Cardiac metastasis of a concealed metastatic lung carcinoma. (A) CMR myocardial tissue characterisation. A T2-weighted with fat saturation sequence in the long-axis view shows multiple hyperintense nodules; (B) an inhomogeneous uptake of gadolinium agent on postcontrast delayed T1 inversion recovery in the same section. Note the multiple nodules involving the full interventricular septum; (C) transbronchial biopsy. Histology reveals diffuse infiltration of irregularly shaped glands with cytological atypia (inset); (D) marked cytoplasmic immunoreactivity for CK7 is visible at immunohistochemistry; (E) whitish firm metastatic nodules are visible in transverse section of the heart at postmortem; (F) at histology, the nodules consist of neoplastic epithelial tissue proliferation (inset).From Perazzolo Marra et al., Circulation, 2012.*

Abdominal and pelvic tumors may reach the right atrium through the IVC. The most common tumor exhibiting this tendency is renal cell carcinoma (4). A recent review suggested that in men, lung cancer is the most frequent cause of cardiac metastasis, followed by esophageal cancer and lymphoma, whereas in women, lung cancer is the most frequent, followed by lymphoma and breast cancer (5).

Pathologic findings

Metastatics deposits may be diffuse, multinodular, or consist of a single dominant mass. Especially with carcinomas, there may be diffuse studding and thickening of the pericardial surfaces. This pattern can grossly be confused with mesothelioma, or benign fibrosing pericarditis. Carcinomatous spread in the myocardium is frequently most prominent in subepicardial lymphatics, whereas melanomas, sarcomas, renal cell carcinomas, lymphoid neoplasms and intramyocardial interstitial tumours. The histopathologic distinction between primary and metastatic sarcoma may be impossible upon surgical resection of a cardiac tumour. However sarcomas metastatic to the heart cause symptoms at their primary site before cardiac symptoms are evident, however. Although primary sarcomas of the heart are uncommon, extracardiac sarcomas presenting as cardiac metastases are even rarer. Heart failure, cardiac arrhythmias, heart blocks, acute myocardial infarction, myocardial rupture, systemic embolization, and superior vena cava (SVC) syndrome (*Figure 10.2*) are other manifestations of cardiac metastases. A new heart murmur or any new ECG finding without clear symptoms in a cancer patient should raise suspicion for cardiac metastases. Typical ECG findings encountered in patients with cardiac metastases are ST-T wave changes (mimicking myocardial ischemia or injury), new atrial fibrillation or flutter, and low voltages, with electrical alternans indicating a significant pericardial effusion. ECG findings of myocardial injury may indicate invasion or compression of the coronary vessels by tumor (4).

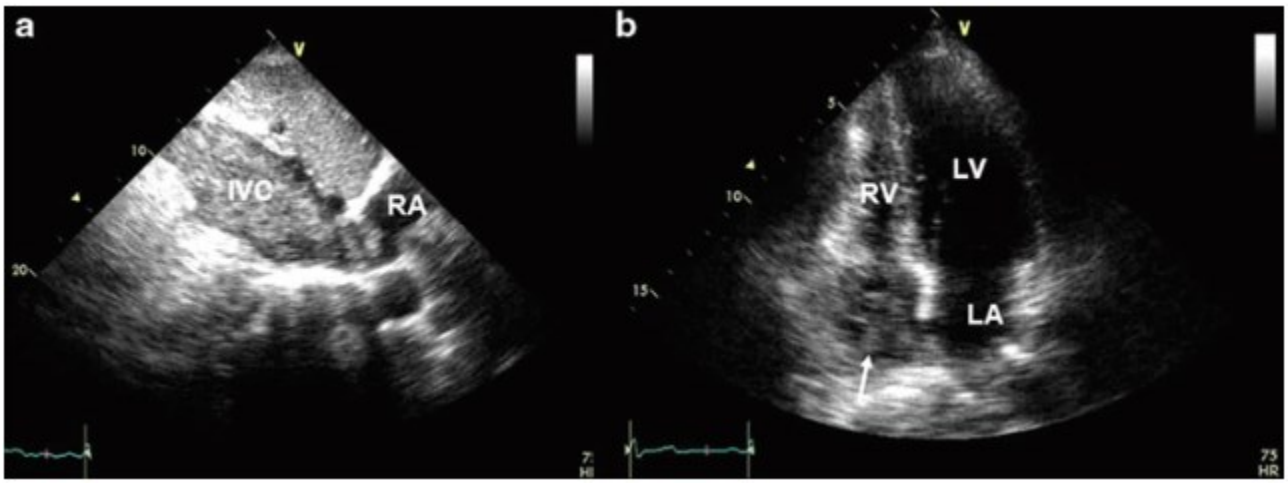

Figure 10.2 *Renal cell carcinoma (hypernephroma). A large hyperdense mass, filling almost completely the lumen of inferior vena cava and protruding into right atrium (arrow), can be appreciated at transthoracic echocardiography from both subcostal (**a**) and apical four-chamber view (**b**) IVC inferior vena cava, LA left atrium, LV left ventricle, RA right atrium, RV right ventricle. From Basso et al., Cardiac Tumor Pathology, 2013.*

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CHAPTER 11

DIRECT AND INDIRECT COMPLICATIONS OF NEOPLASIA

11.1 Cardiac Tamponade

Approximately a third of patients with cardiac tumors have a pericardial involvement will initially be found to have impaired cardiac function, that can progress to cardiac tamponade, which demands immediate drainage. Symptoms include chest pain, fever, dyspnea, cough, and peripheral edema. Tamponade without two or more signs of an inflammatory process (typically pain, friction rub, fever, diffuse ST-segment elevation) is more likely to be malignant (2.9-fold increase in risk)(1). Physical examination, ECG, and chest radiographic findings are generally similar to those of pericardial effusion of any cause. Echocardiography demonstrates the effusion, which is usually large, although it does not have to be if the fluid has accumulated quickly. However, tamponade can occur with loculated effusions, and in these cases the typical echocardiographic signs may be absent. Acute treatment of tamponade includes careful fluid replacement as a temporizing measure if the patient is believed to be volume depleted with compromised hemodynamics (1). Echocardiography-guided pericardiocentesis is required. Fluid should be sent for a full battery of diagnostic tests because as noted, the cause is commonly noncancerous, even in patients with known cancer. If the effusion is malignant, cytologic examination of the pericardial fluid is positive in approximately 85% of patients. Although no randomized clinical trials using various strategies have been conducted, the risk for recurrence of the effusion appears to be reduced by extended catheter drainage (3 ± 2 days; 11.5% recurrence) as opposed to simple pericardiocentesis (2). Recurrence of pericardial effusion can often be treated by repeated pericardiocentesis and extended catheter drainage. Some have used intrapericardial instillation of chemotherapeutic agents or sclerosing agents, but it is not clear that this approach is more effective than extended catheter

drainage. Occasionally, percutaneous balloon pericardiotomy or pericardiectomy may be required, but patients with malignant effusions have such a poor prognosis (median survival of 135 days in one series of 275 patients) that invasive procedures should be avoided, if possible. Therapy is directed at the underlying tumor.

11.2 Pericardial neoplastic involvement

The differential diagnosis between malignant processes and other causes of pericarditis is particularly relevant and generally is accomplished by imaging, CT scan, cytology of pericardial fluid and eventually biopsies. Primary tumours of the pericardium, either benign (lipomas and fibromas) or malignant (mesotheliomas, angiosarcomas, fibrosarcomas), are very rare (3,4). Mesothelioma, the most common malignant tumour, is almost always incurable. The most common secondary malignant tumours are lung cancer, breast cancer, malignant melanoma, lymphomas and leukaemias. Malignant pericardial effusions may be small, medium or large, with an imminent tamponade (frequent recurrences) or constriction; they may even be the initial sign of malignant disease (5). The diagnosis is based on confirmation of the malignant infiltration within the pericardium (3,4). Of note, in almost two-thirds of patients with documented malignancy, pericardial effusion is caused by non-malignant diseases, radiation pericarditis (breast cancer and Hodgkin disease) , other therapies or opportunistic infections (4,6).

11.3 Superior Vena Cava Syndrome

In the midthird of the mediastinum, the left and right brachiocephalic veins join to form the SVC. The SVC then extends caudally, courses anterior to the right main bronchus, and terminates in the superior aspect of the right atrium. The SVC is joined posteriorly by the azygos vein and runs

posterior to and to the right of the ascending aorta. During its course the SVC is adjacent to the right paratracheal, azygous, right hilar, and subcarinal lymph node groups. Blood flow in the venous system is under low pressure and the vessel itself is thin walled. Any inflammatory process in the mediastinum or enlargement of the lymph nodes or ascending aorta can cause the SVC to be compressed and result in reduced blood flow and eventually complete occlusion (*Figure 11.1*).

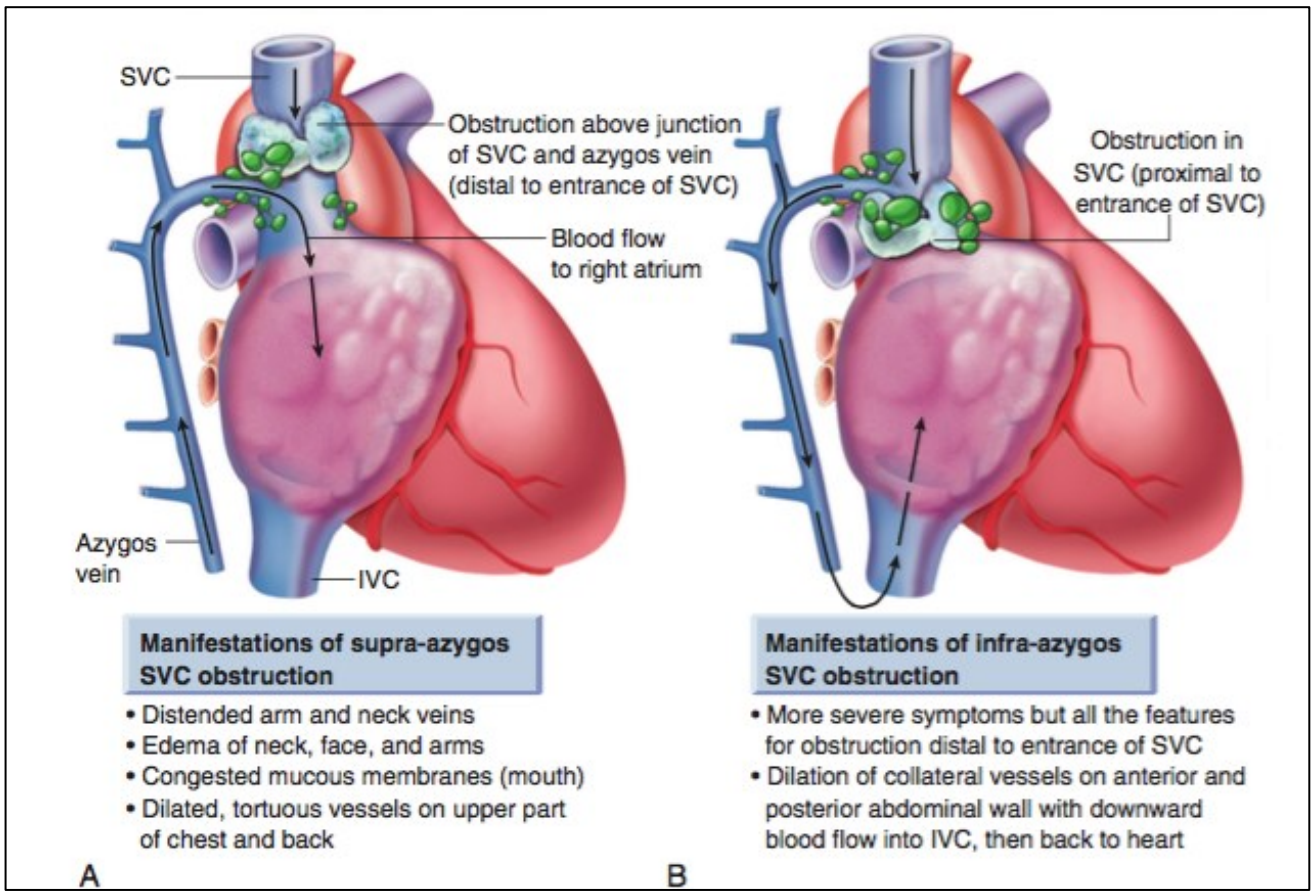

Figure 11.1 *Anatomy of SVC syndrome. Lymph nodes may obstruct blood return above the entrance of the azygos vein* ***(A)*** *and result in edema of the face, neck, and arms and distended veins in the neck and arms and over the upper part of the chest. Obstruction below the return of the azygos vein* ***(B)*** *results in retrograde flow through the azygos via collateral veins to the IVC and in all the symptoms and signs in* ***A*** *plus dilation of the veins over the abdomen as well. From Skatin AT Atlas of Diagnostic Oncolog, 2003.*

SVC syndrome was first described by William Hunter in 1757 in a patient with a syphilitic aneurysm of the ascending aorta. Over time, vascular causes have declined and now the most

common cause of SVC syndrome is malignancy, of which lung carcinoma is the most frequent, followed by lymphoma and metastatic cancer (7). Malignancy accounts for more than 85% of cases of SVC syndrome (8). Other causes of SVC syndrome, which are somewhat benign, account for 3% to 15% of cases and include nonmalignant causes such as thrombosis from the use of intravascular devices (e.g., catheters or pacemakers), infection, thymoma, substernal thyroid goiter, and aortic aneurysm (8). Other possibilities include disease causing systemic vasculitis, such as Behçet disease, and radiation-induced fibrosis. A clinical diagnosis is usually made on the basis of a constellation of symptoms and signs, and a classification system has been proposed (9). The development of SVC syndrome is generally insidious, but occasionally it may develop rapidly. The severity of the syndrome depends on the rapidity of onset of the obstruction and its location. The more rapid the onset, the more severe the symptoms because collateral veins do not have time to distend and accommodate the increased blood flow. A typical manifestation consist of facial edema, dyspnea, and cough (7,10). Facial edema is seen most frequently; it is worse in the morning and gets better during the day as the patient ambulates. Other symptoms that occur less frequently include stridor, headache, syncope, dizziness, hoarseness, and confusion (7,10). Common findings on examination include facial edema, distended neck and chest veins, arm edema, and facial plethora (7). Investigations depend primarily on whether the underlying cause is known. In a patient with no previous diagnosis, a chest radiograph, CT of the chest, and potentially bronchoscopy may reveal lung cancer as the most common cause. CT is usually very helpful because it provides a detailed evaluation of the venous system and also helps identify the principal causes, such as a neoplasm, thrombosis from central catheters, or infection resulting in sclerosing mediastinitis (11). Magnetic resonance venography can be used as an alternative to CT in patients with an allergy to contrast dye or in whom CT cannot be performed for other reasons. Intravenous venography is another option in patients who may not be able to undergo CT. Treatment is directly related to the underlying cause. In patients with known malignancy, systemic chemotherapy and radiation therapy are typically carried out. If the main cause of SVC obstruction is thrombosis, stent deployment is an

attractive option (12,13). Surgical bypass of an obstructed SVC is another option, especially if insufficient diagnostic tissue can be obtained by other measures.

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CHAPTER 12

SURGICAL TREATMENT of CARDIAC TUMORS

As soon as the diagnosis of cardiac tumor is confirmed, the patient should be treated at an interdisciplinary center. It is crucial for oncologists, radiotherapists, and surgeons to cooperate closely as a team. Cardiac tumors present a particular challenge for heart surgeons, because great versatility is required. The treating cardiac center must have experience over the whole spectrum of heart surgery, including adult, pediatric, and rhythm surgery as well as transplantation and artificial heart implantation. Owing to the small numbers of cases there is no evidential basis for the optimal treatment regime, especially when it comes to malignant tumors (1).

12. 1 Surgical tecniques

The surgical management of cardiac tumors began in 1936 when Beck successfully resected a teratoma external to the right ventricle (2). In 1951 Mauer resected a left ventricular lipoma (3) and Bhanson and Newman in 1952 removed a large right atrial myxoma using inflow caval occlusion (4). In 1954 Crafoord for the first time removed successfully a left atrial myxoma using cardiopulmonary bypass (5), whereas Kay et al. first removed a left ventricular myxoma in 1959 (6). By the early sixties, owing to the progressive safety of cardiopulmonary bypass and to the increased use of echocardiography, atrial myxomas started to be removed successfully on a more routine-based approach (7,8). Currently, operative excision is the treatment of choice for most benign cardiac tumors, very often resulting in a complete cure. Through a median sternotomy, intramural and intracavitary tumors must be excised under direct vision using the heart–lung machine (*Figure 12.1*) with bicaval or femoral cannulation.

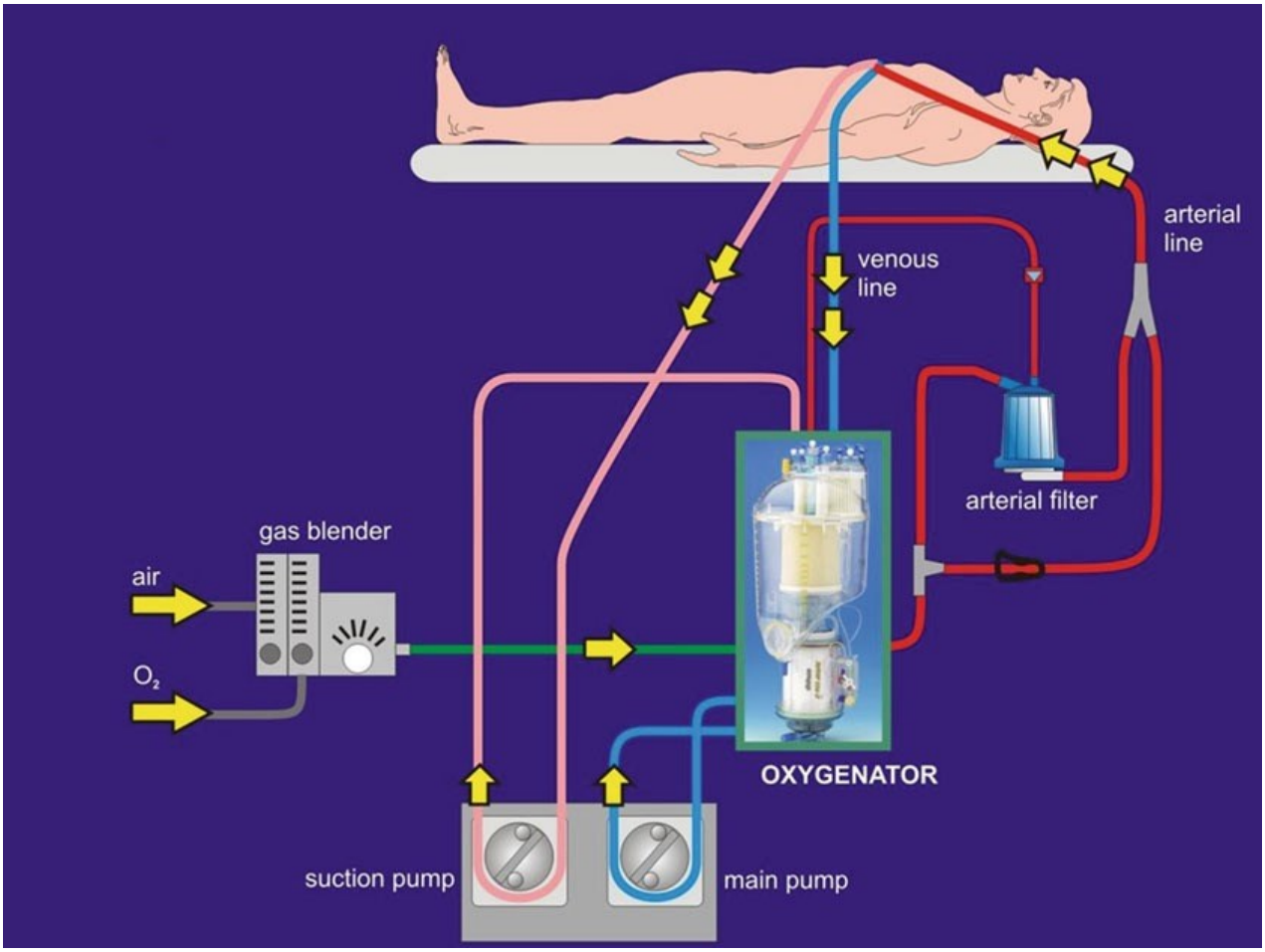


Figure 12.1 *Diagram of a cardiopulmonary bypass circuit. Venous blood is drained from the venae cavae/right atrium into the venous reservoir which is incorporated in the membrane oxygenator/heat exchanger unit. Arterialized blood exits the oxygenator and passes through a filter/ bubble trap to the aortic cannula, which is usually placed in the ascending aorta. Suction systems and sources of gases are also represented. From Basso et al., Cardiac Tumor Pathology, 2013.*

After establishing cardiopulmonary bypass, under mild hypothermia, the heart is separated from the systemic circulation by an aortic cross-clamp followed by the infusion of blood or crystalloid cardioplegia administered antegradely into the aortic root, and/or retrogradely into the coronary sinus. Although some epicardial tumors may be removed without the aid of extracorporeal circulation, intramural and intracavitary tumors must be excised under direct vision. The surgical approach will depend on the location of the cardiac mass (right, left, combined atriotomy, aortotomy, etc.). In view of the potential multifocal location of the cardiac tumors, all the cardiac chambers will need to be systematically explored. A good surgical exposure represents the fundamental principle to accomplish a complete, possibly *en bloc,* resection of the tumor. The ideal

resection aims to include the tumor and a portion of the cardiac wall and/or interatrial septum, to which it is attached, spared by the disease. To overcome the technical challenges of complete resection with accurate cardiac reconstruction, particularly of left-sided tumors with posterior extension, a technique of cardiac explantation, ex vivo tumor resection with cardiac reconstruction, and cardiac reimplantation cardiac autotransplantation has been successfully utilized (9-11). Every care should be taken to remove the tumor without fragmentation. The use of an intra-aortic filter (Edwards Embol-X System, Edwards Lifescience, Irvine CA) may help to reduce the event of systemic embolization in case of friable tumors located in the left cardiac chambers (12). Ventricular tumors are usually approached through the AV valves if located in the ventricular inflow, or through the semilunar valves when located in the ventricular outflow tract. In the event of tumors involving a cardiac valve, the surgical strategy should still aim to a complete resection of the mass, although trying to preserve the native valve by means of several well-described reparative techniques. When this is not possible, a valve prosthesis may be used.

Simple tumor resection

Simple resection is generally selected for benign tumors such as myxomas. Care must be exercised in connecting the heart–lung machine to avoid dislodging any tumor material. For this reason we open both atria from the right superior pulmonary vein without injuring the tumor or its base. The tumor and its root can then be removed from the septum in toto. We always inspect all the chambers of the heart to exclude the presence of further tumors (13). The defect is closed with patch material. Apart from the usual risks involved in the use of a heart–lung machine this intervention is relatively uncomplicated.

Complex tumor resection

Complex tumor resection is possible to provide when the mass is confined to the heart and, if malignant, has not infiltrated the adjacent tissues. In advanced tumors involving the right side of the

heart the whole right half of the organ can be resected. Pulmonary blood flow is assured by means of Fontan circulation, well known from pediatric heart surgery (13, 14). Chronic right heart failure may result.

Ex-situ resection

In the event that the tumor involves the posterior wall of the left atrium or the dorsal great vessels, the heart can be removed from the thorax to facilitate complete resection. Attempts at conventional surgery in such circumstances are hampered by an inadequate view of the tumor, leading to incomplete resection and an unfavorable long-term outcome. Lifting the heart out of the body means it can be turned for optimal visualization of all structures. Following tumor resection the cardiac anatomy is restored using artificial materials (prostheses, patches, valves) or biological tissue before the heart is reimplanted (*Figure 12.1*) (15-18). Depending on the amount of cardiac tissue excised, left and/or right heart failure may result as a secondary complication.

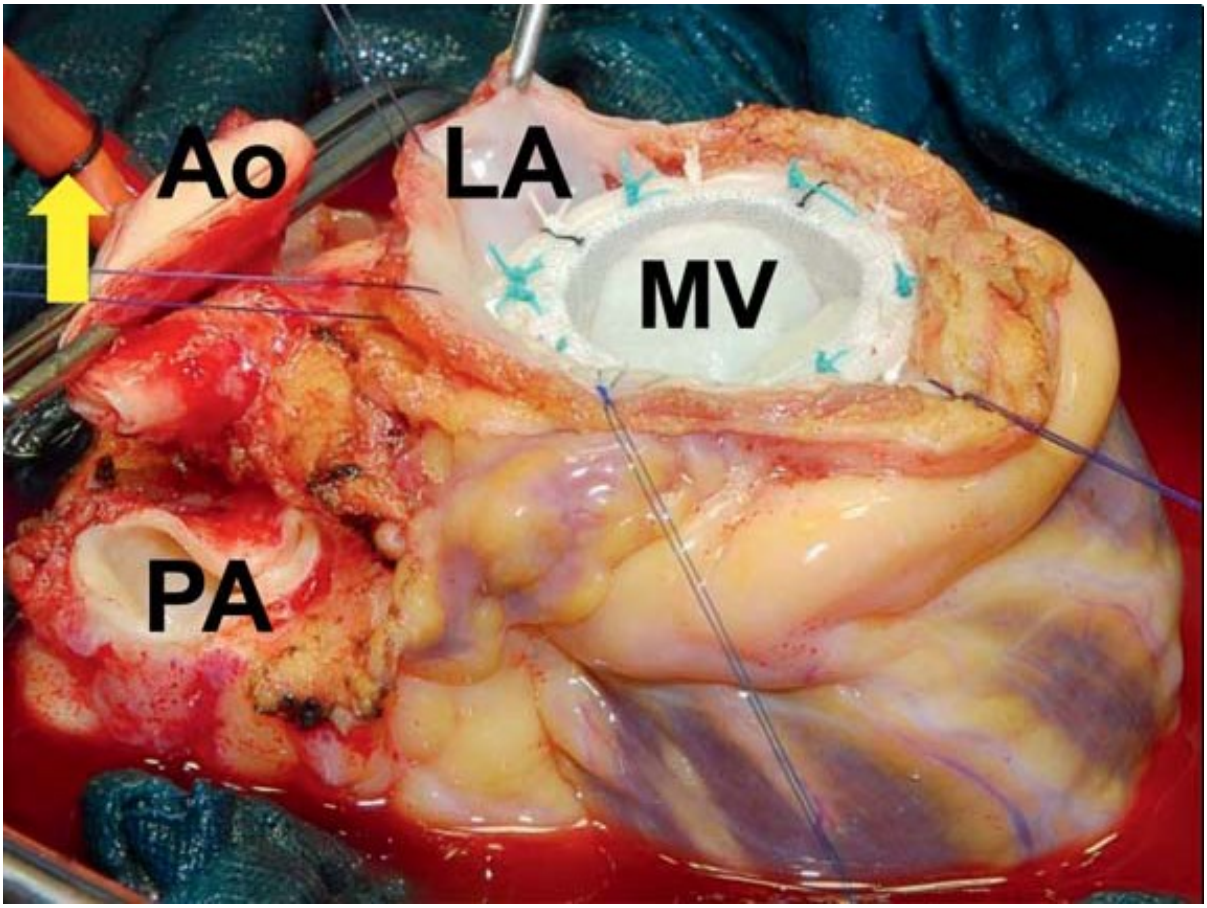
Implantation of an artificial heart

If the tumor also involves the left heart, and there are no metastases, the implantation of a total artificial heart (TAH) can be considered as a treatment of last resort—especially in younger patients. The principal complications following successful implantation are hemorrhages, thromboses, infections, and, as a result of the necessary anticoagulation, embolisms (19).

Heart transplantation

Heart transplantation (HTx) can occasionally be considered as a final treatment option in individual cases, provided distant metastases can be ruled out (19). One significant risk of this procedure is the danger of exacerbation of undetected micrometastases by the necessary immunosuppression.

Figure 12.1 *Explanted heart after ex-situ resection of a sarcoma and implantation of a mitral valve (MV) before cardiac reimplantation (LA, resection margin, left atrium; Ao, aorta; PA, pulmonary artery; arrow, cardioplegia catheter). From Hoffmeier A, et al., Dtsch Arztebl Int, 2014.*



12.2 Surgical Benign Tumors

a. Myxoma

Surgical resection is the only effective therapeutic option for patients with cardiac myxoma and should not be delayed because death from obstruction to flow within the heart or embolization may occur in as many as 8% of patients awaiting operation (20-22). A median sternotomy approach with ascending aortic and bicaval cannulation usually is employed (*Figure 12.2*). Manipulation of the heart before initiation of cardiopulmonary bypass is minimized in deference to the known friability and embolic tendency of myxomas. Left atrial myxomas can be approached by an incision through the anterior wall of the left atrium, anterior to the right pulmonary veins, eventually extended behind both cavae to achieve greater exposure. Exposure of left atrial myxomas is maximized by using several principles from mitral valve repair surgery. Removal of large tumors attached to the interatrial septum however may be facilitated by a right atrial approach, which allows easy removal of tumor attached to the fossa ovalis with full-thickness and large excision at the site of attachment and easy patch closure of the atrial septum if necessary (*Figure 12.3, 12.4,12.5, 12.6*) (23). As mentioned, the tumor should be removed without fragmentation. Nevertheless, after removal the surgical field should be irrigated and inspected for loose fragments. In case of atrial wall rather than septal attachment, large full-thickness excision of tumor insertion should be aimed whenever possible. A systematic inspection of the other cardiac chambers to exclude other tumor location potentially overlooked by the utilized imaging techniques is always recommended.

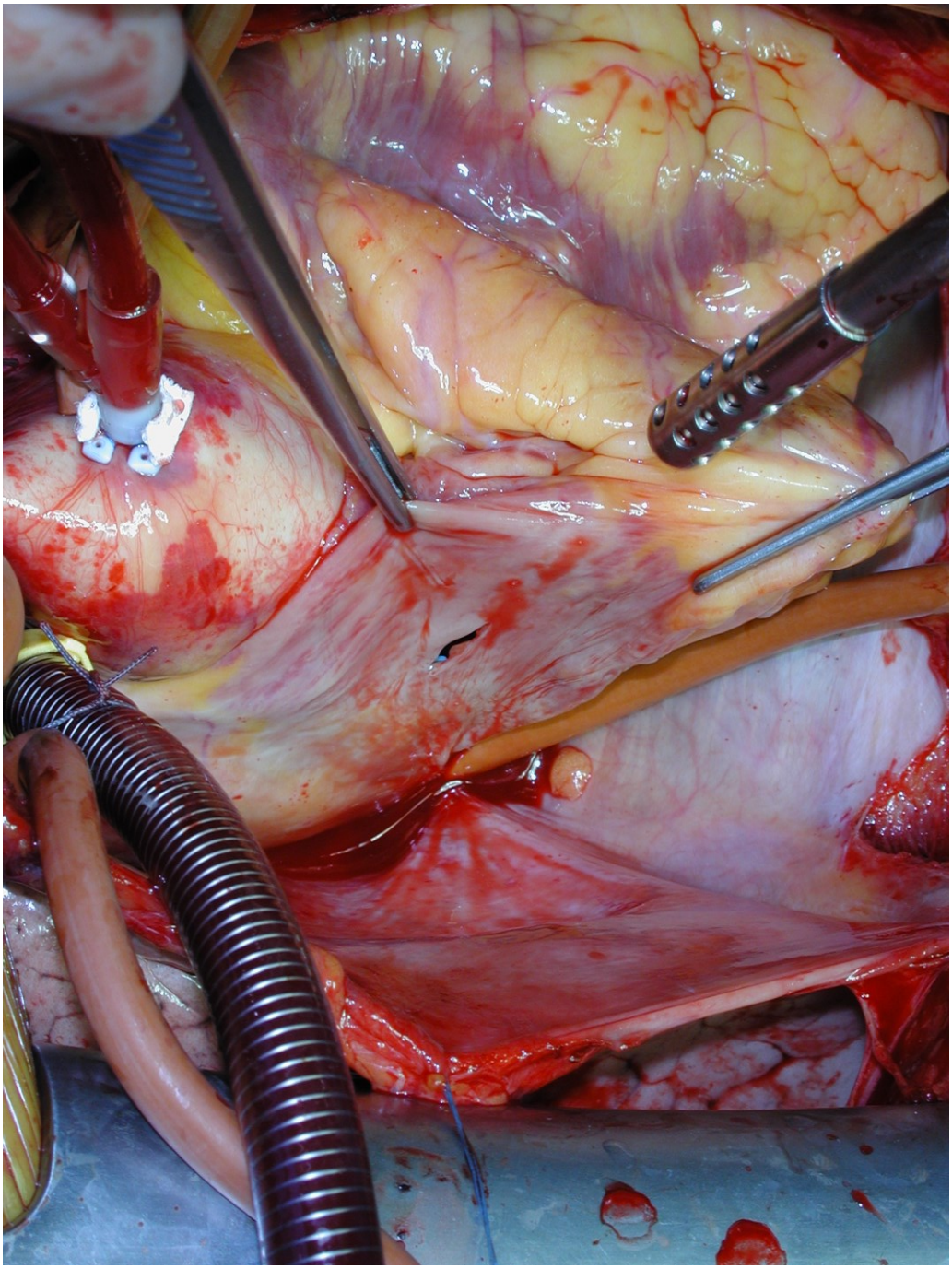


Figure 12.2 *Standard venous cannulation for atrial myxomas and right arteriotomy site for left atrial myxoma. Superior vena cava cannulation allows increased right atrial exposure or division of superior vena cava for additional left atrial exposure.*

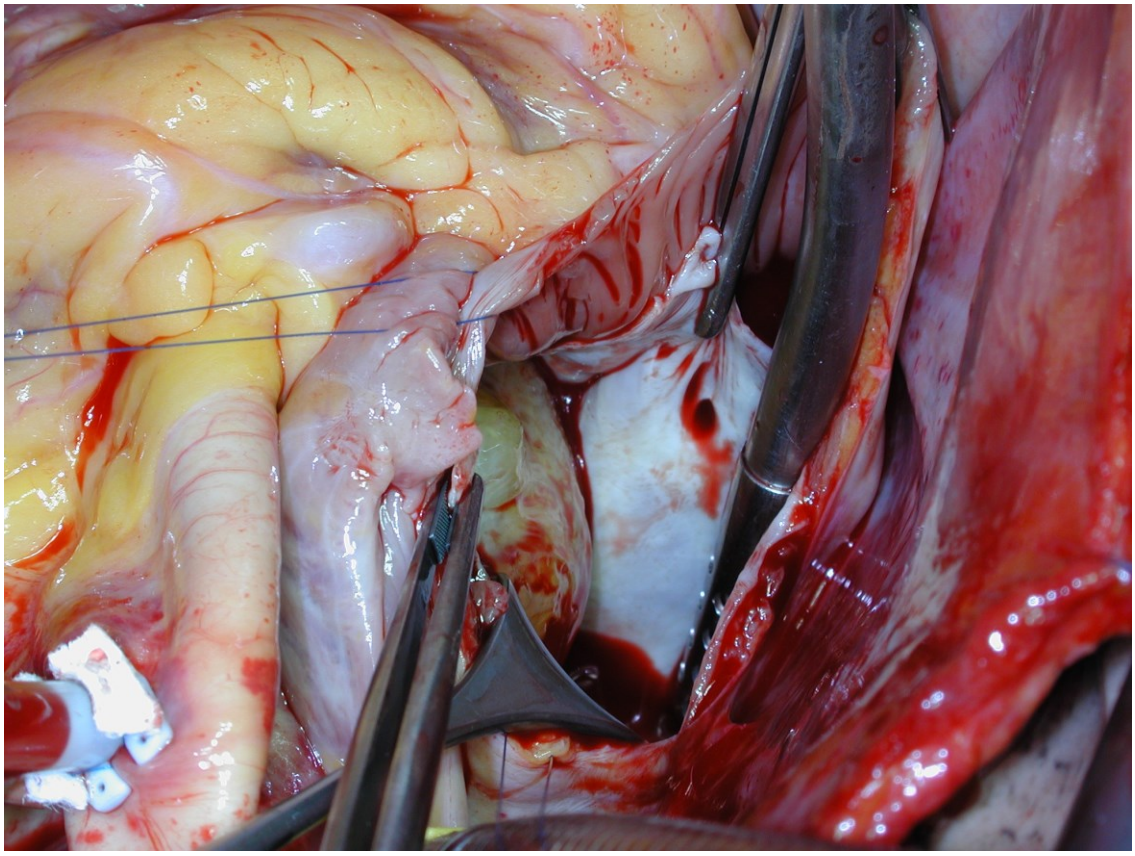


Figure 12.3 *Left atriotomy and exposure of myxoma.*

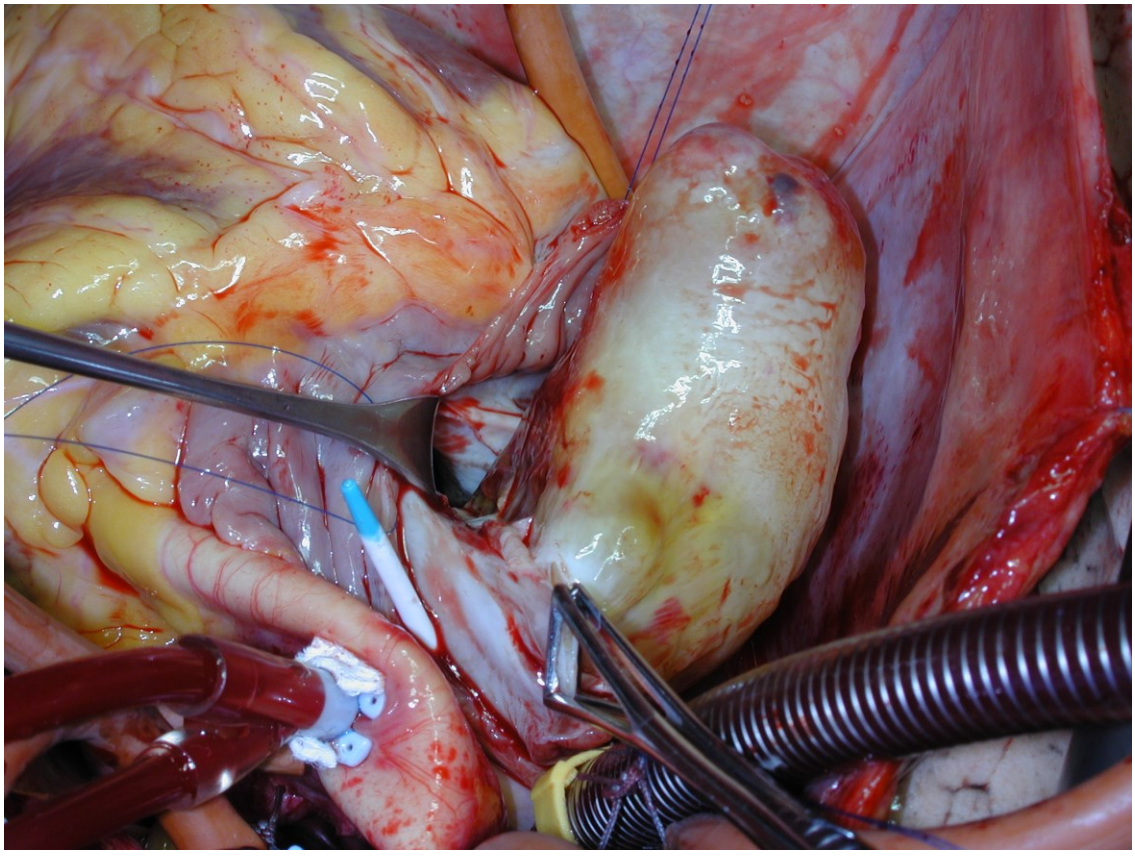


Figure 12.4 *Removal of large left atrium myxoma.*

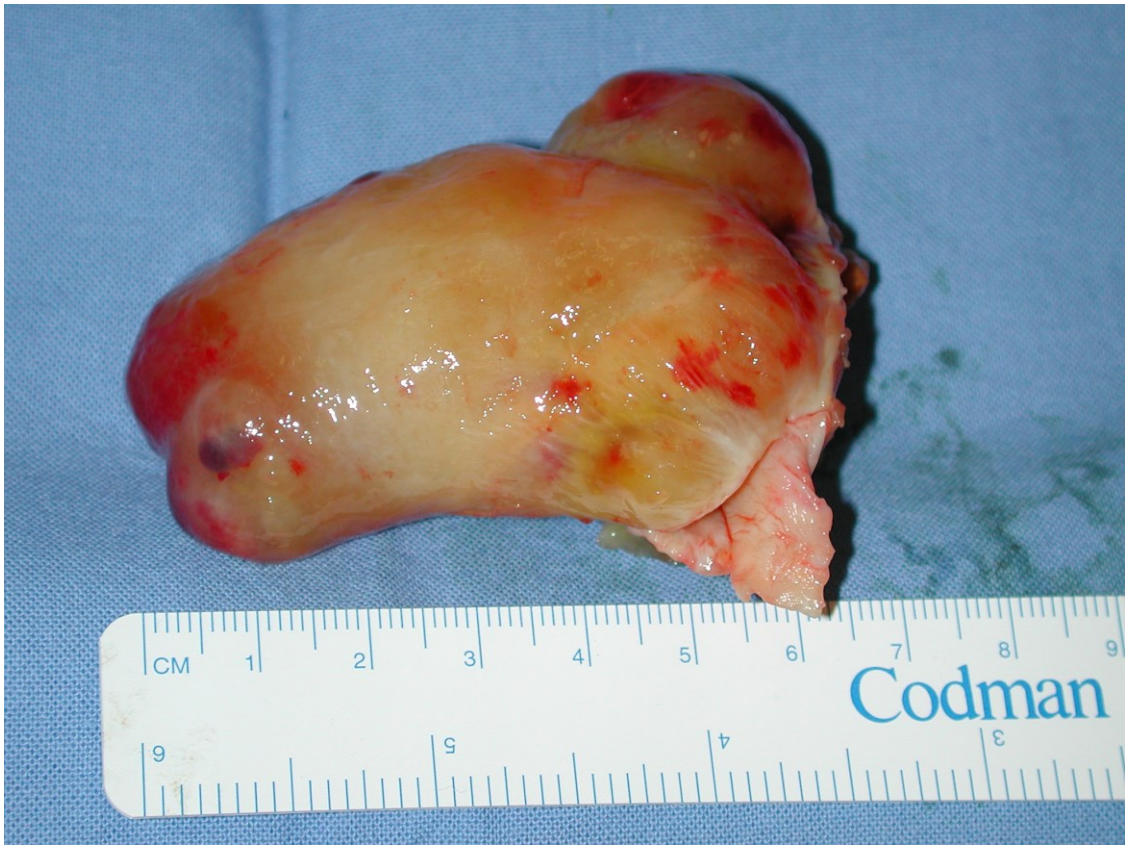


Figure 12.5 *Left atrium myxoma.*

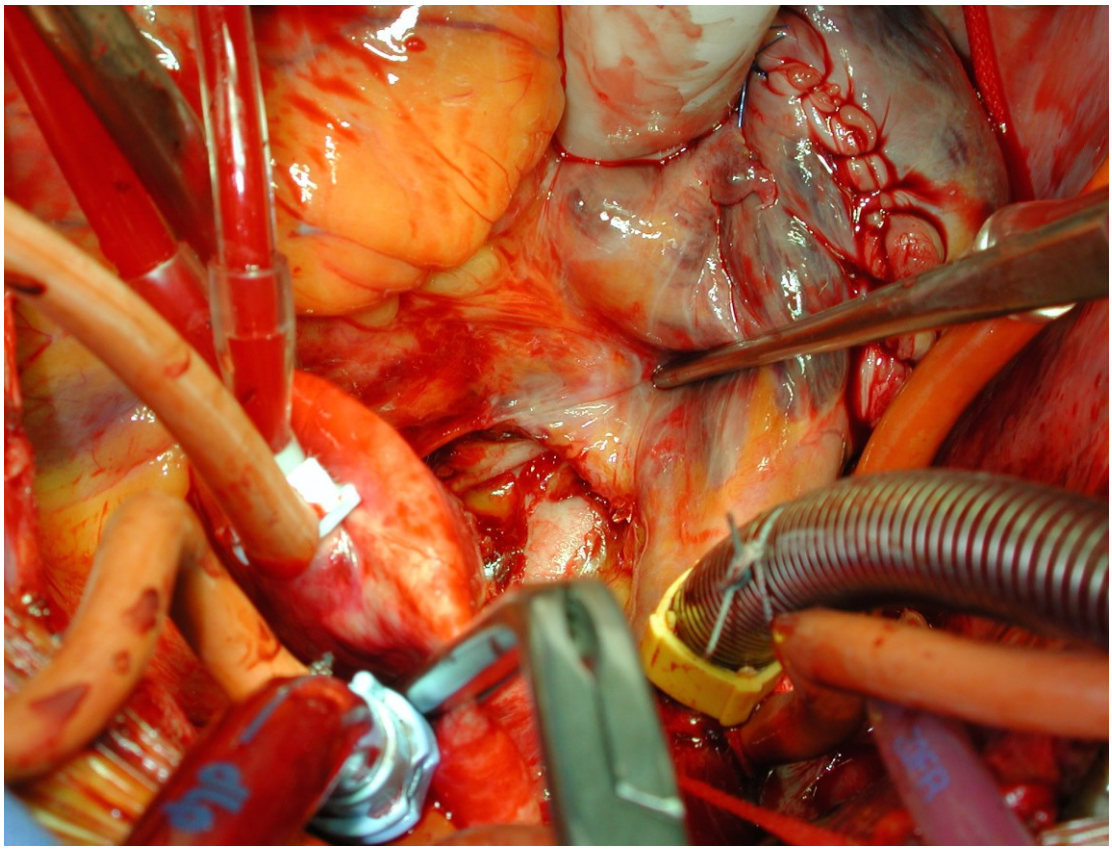


Figure 12.6 *Repair of atrial septum with pericardial patch after removal of myxoma*

About 10 to 20% of all cardiac myxomas are found in the right atrium (24). Right atrial myxomas pose special venous cannulation problems, and intraoperative echocardiography may be of benefit in allowing safe cannulation. Both venae cavae may be cannulated directly. When low-or high-lying tumor pedicles preclude safe transatrial cannulation, cannulation of the jugular or femoral vein can provide venous drainage of the upper or lower body. In general, we always can cannulate the superior vena cava distal enough from the right atrium to allow adequate tumor resection, but occasionally femoral venous cannula drainage has been necessary for low-lying right atrial tumors encroaching on the inferior vena caval orifice. If the tumor is large or attached near both caval orifices, peripheral cannulation of both jugular and femoral veins may be used to initiate cardiopulmonary bypass and deep hypothermia. The right atrium may be opened widely for resection of the tumor and reconstruction of the atrium using pericardium or polytetrafluoroethylene, keeping in mind that resection of large or critically placed right atrial myxomas may require careful preoperative planning and special perfusion strategies. Because myxomas rarely extend deep in the endocardium, it is not necessary to resect deeply around the conduction tissue. The tricuspid valve and the right atrium, as well as the left atrium and ventricle, should always be inspected carefully for multicentric tumors in patients with right atrial myxoma, with or without familial occurrence (23,25,26). The surgeons policy is to resect full thickness whenever possible. However, only partial-thickness resection of the area of tumor attachment has been performed when anatomically necessary without a noted increase in recurrence rate (27,28). Ventricular myxomas (6–8%) occur more often in women and children and may be multicentric (29-33). Right ventricular tumors typically arise from the free wall, and left ventricular tumors tend to originate in the vicinity of the posterior papillary or at the apex (32). Ventricular myxomas usually are approached through the atrioventricular (AV) valve or by detaching the anterior portion of the AV valve for exposure and resection and reattachment after resection (34). Occasional small tumors in either outflow tract can be removed through the outflow valve (34,35). If necessary, the tumor is excised through a direct incision into the ventricle, but this is unusual. It is not necessary to

remove the full thickness of the ventricular wall because no recurrences have been reported with partial thickness excisions. As with right atrial myxoma, the presence of ventricular myxoma prompts inspection for other tumors because of the high incidence of multiple tumors. Overall 30-day mortality after removal of an atrial myxoma is below 5%, although excision of ventricular myxomas carries a higher risk (approximately 10%). Operative mortality may be increased by tumor unrelated variables such as advanced age, disability, and/or comorbidities. Long-term survival, freedom from complication, and quality of life are excellent in the nonfamilial form of myxoma (36, 14, 23, 25, 28, 36, 37). The recurrence of an intracardiac myxoma (described by 6 months and up to 11 years after the resection) may be related to an inadequate original resection, when at the same site of the original tumor, or to the presence of neoplastic fragments. Recurrence of nonfamilial sporadic myxoma is approximately 1–4% and possibly lower in patients with a normal DNA genotype (28,38). The rarer subgroup of patients with sporadic myxoma and abnormal DNA have a recurrence rate estimated at between 12 and 40%. The recurrence rate is highest in patients with familial complex myxomas, all of whom exhibit DNA mutation (38). Overall, recurrences are more common in younger patients. Most recurrent myxomas occur in the same or different cardiac chambers, and may be multiple particularly in familial complex myxomas. Extracardiac recurrence after myxoma excision, likely from embolization, with local tumor growth, and invasion, has been observed in the brain, arteries, soft tissue, and bones (24).

b) Minimally invasive approaches to surgical removal

Minimally invasive approaches are being applied with increasing frequency in all areas of cardiac surgery, and cardiac tumors are no exception. Experience is confined to benign tumors and is quite limited. Approaches have included right parasternal or partial sternotomy exposure with standard cardioplegic techniques (39), right submammary incision with femoral-femoral bypass and nonclamped ventricular fibrillation (40) and the right submammary port access method with antegrade cardioplegia and ascending aortic balloon occlusion (41). Minimally invasive cardiac surgery may be used in a selected group of patients with cardiac tumors *(Figure 12.7, 12.8)*. Thoracoscopic techniques have been used to aid in visualization and removal of ventricular fibroelastomas (42,43). There have been case reports of myxoma removal via thoracoscopy (44,45). It is important to remember that use of a minimally invasive technique must not compromise complete surgical excision. Results in this limited number of selected patients have been good, but more experience and longer follow-up are needed before this can be recommended as a standard approach.

Figure 12.7 *Minimally invasive cardiac surgery.*

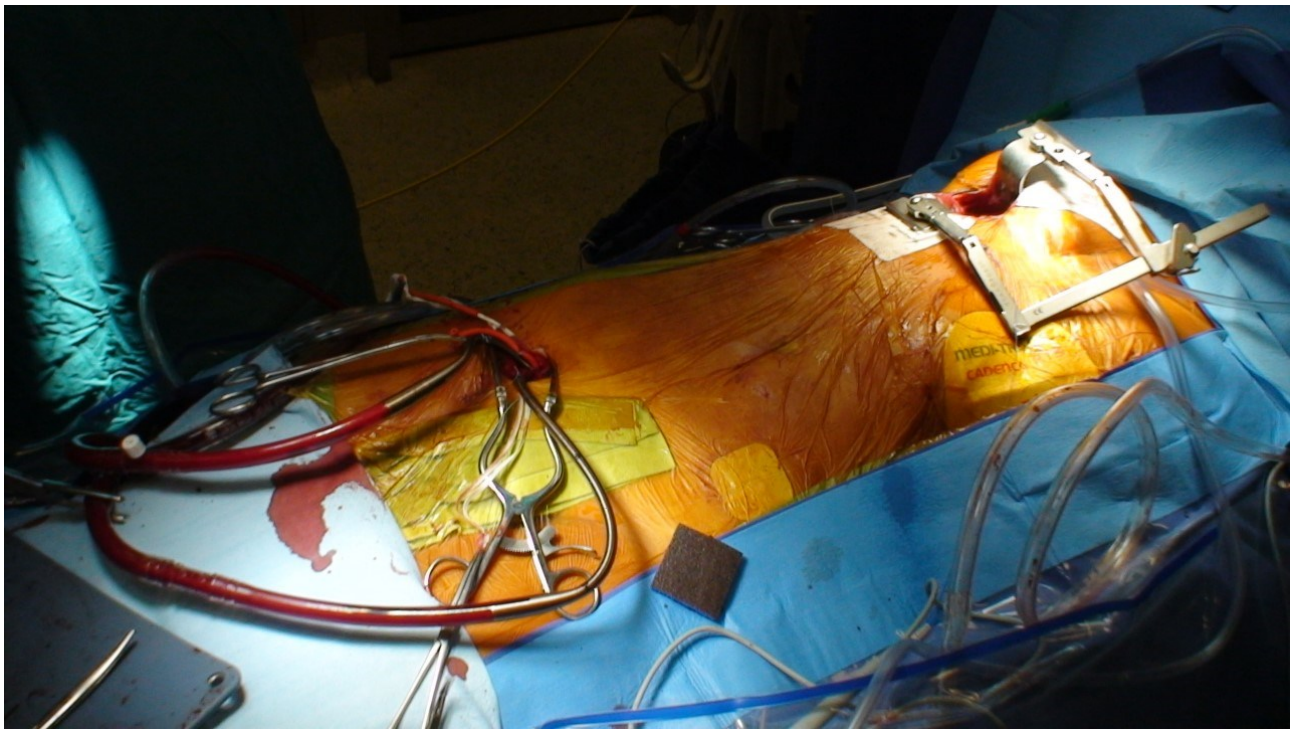
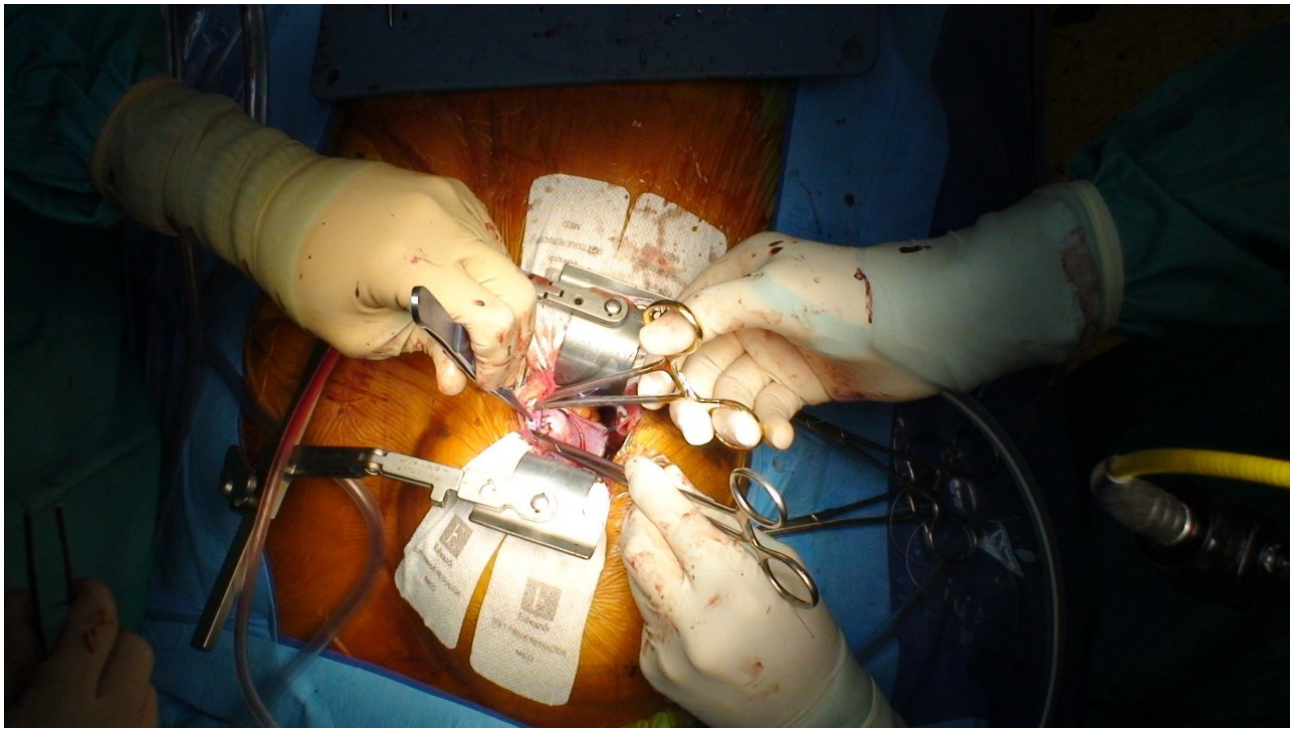


Figure 12.8 *Minimally invasive cardiac surgery for removal cardiac myxoma.*



12.3 Other Benign Cardiac Tumors

Large tumors that produce severe symptoms should be resected. Smaller, asymptomatic tumors encountered unexpectedly during cardiac operation should be removed if excision can be performed without adding risk to the primary procedure. These tumors are not known to recur.

a. Papillary Fibroelastoma

Papillary fibroelastomas are the most common tumors of the cardiac valves, accounting for 75% of all valvular tumors. Papillary fibroelastomas of the cardiac valve, affect mainly the aortic or the mitral valve, even though tricuspid and pulmonary valves may also be affected, should be resected whenever diagnosed because of their known tendency to produce life-threatening complications. Valve repair rather than replacement should follow the resection of these benign tumors whenever technically feasible, using conservative margins of resection (*Figure 12.9,12.10*). Occasionally, papillary fibroelastomas locate in the left ventricle, more often in the outflow tract, can be multifocal, and are associated with the hypertrophic obstructive cardiomyopathy (46-48).

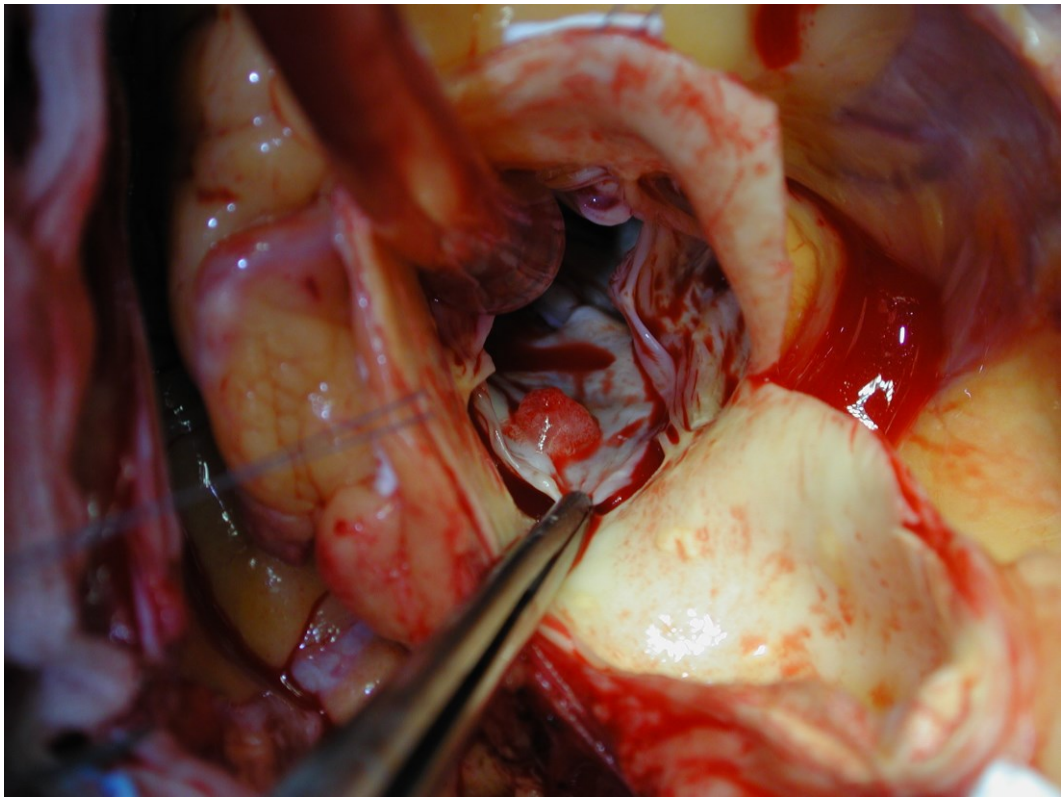


Figure 12.9 *Resection of aortic Papillary Fibroelastoma.*

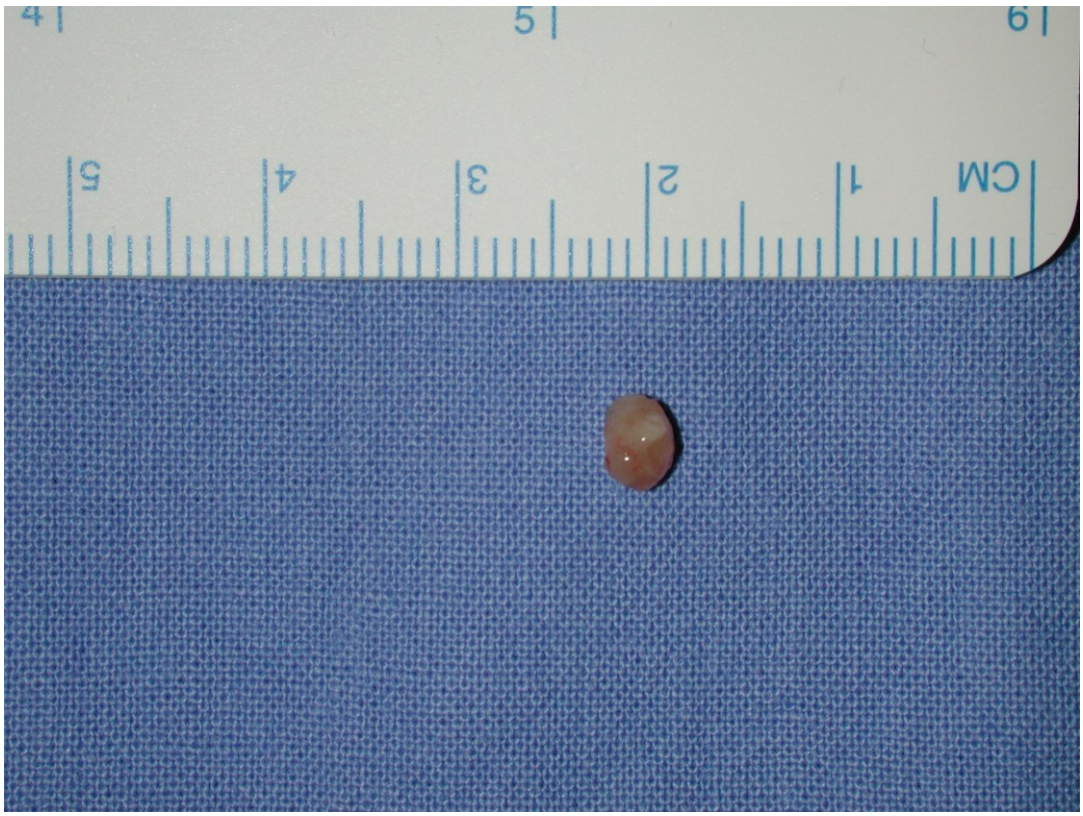


Figure 12.10 *Aortic Papillary Fibroelastoma.*

b. Lipoma

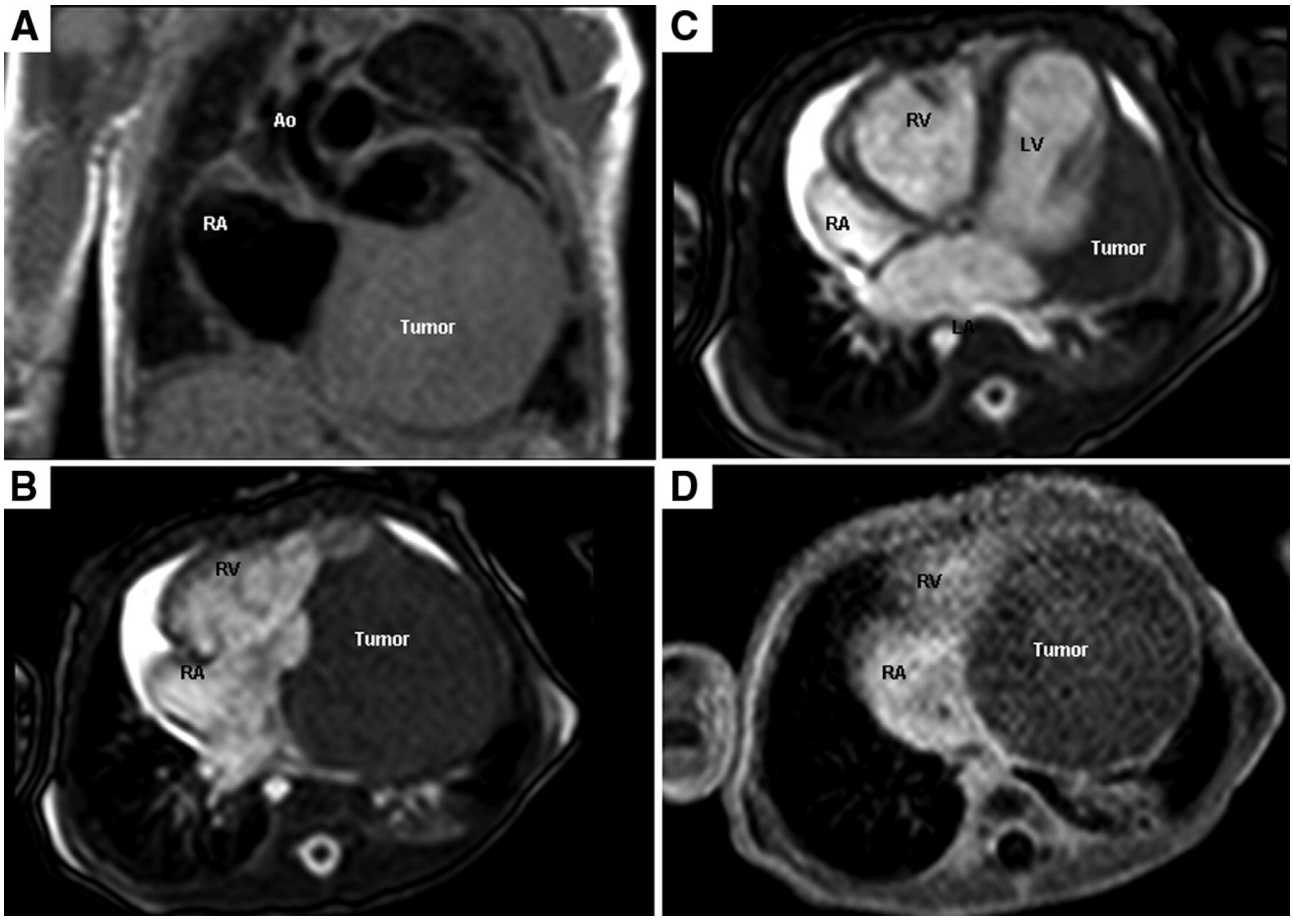
Lipomas are well encapsulated primary benign cardiac tumors, and consist of mature fat cells (29, 49-51). They are usually located in the subepicardium, in the left ventricle, in the right atrium, and in the interatrial septum. The non-encapsulated hypertrophy of the fat within the atrial septum, often in continuity with the epicardial of the right AV sulcus, is known as *lipomatous hypertrophy*. Large lipomas, particularly when associated with severe symptoms, should be resected. Smaller, asymptomatic tumors, incidentally discovered during cardiac operation undertaken for different indications, should be removed if excision is doable without adding risk to the primary procedure. In case of location in the atrial septum, patch reconstruction may be necessary. Cardiac lipomas are not known to recur.

c. Rhabdomyoma

Rhabdomyoma represents the most common cardiac tumor in children. Thought to be a myocardial hamartoma rather than a true neoplasm (52, 53), it usually presents during the first few days after birth. Occasionally sporadic, it is quite often associated with tuberous sclerosis (hereditary disorder characterized by hamartomas, seizures, developmental delay and behavioral problems, sebaceous adenomas) (54, 55). Early operation is recommended in patients who do not have tuberous sclerosis before 1 year of age. The tumor usually is removed easily in early infancy, and some can be enucleated. Unfortunately, symptomatic tumors often are both multiple and extensive, particularly in patients with tuberous sclerosis, who, unfortunately, have a dismal long-term outlook. In such circumstances, surgery offers little benefit. The tumor is removed easily in early infancy, and despite being non-encapsulated some can be completely resected. Partial resection may be conceivable to release the obstruction (56). However, whenever planning a surgical strategy, it has to be considered that rhabdomyomas may regress spontaneously after birth, thus limiting indication

to surgical resection to the actual symptomatic cases (*Figure 12.11*)(57).

Figure 12.11 *Cardiac MRI investigation.* ***A****, ECG-triggered breath-hold proton density T1-weighted fast spin echo in coronal plane, showing a large homogeneous isointense mass involving the LV wall.* ***B****, ECG-triggered breath-hold cine steady-state free procession in axial plane, showing the cardiac mass involving the interventricular septum.* ***C****, ECG-triggered breath-hold cine steady state free procession in 4-chamber view, showing no intracardiac obstruction.* ***D****, After gadolinium injection, no mass hyperenhancement is visible. Ao indicates aorta; RA, right atrium; RV, right ventricle; LA, left atrium; LV, left ventricle. From Padalino M. et al., Circulation, 2011.*



d. Fibroma

Fibromas are the second most common cardiac tumor of childhood, although they may also affect the adult population. These are solitary non-infiltrating intramural tumors, usually located in the left

ventricle, mainly in the interventricular septum, and they are often mistaken for hypertrophic cardiomyopathy or apical thrombus.

Surgical excision is successful in some patients, particularly if the tumor is localized, does not involve vital structures, and can be enucleated (58-61).

Video-assisted cardioscopy has been recently reported as a suitable and useful technique to assist removal of primary left ventricular fibroma with intracavitary extension (62). Complete excision is usually curative. On the other hand, partial tumor removal is palliative although often followed by a prolonged survival (63). Children with extensive fibromas, in good overall clinical conditions and with no specific contraindications, have been successfully treated with orthotopic cardiac transplantation (64). In selected cases of extensive right ventricular tumors, a right heart bypass (cavo-pulmonary anastomosis) has also been utilized as a palliative solution or as a *bridge* to orthotopic cardiac transplantation (65).

e. Haemangioma

The tumors can be resected in asymptomatic patients, and cardiopulmonary bypass is recommended. Meticulous ligation of feeding vessels is required to prevent postoperative residual arteriovenous fistulas or intracavity communications. Partial resections have produced long-term benefits. Tumors rarely resolve spontaneously (66,67).

12.4 Surgical Malignant Primary Cardiac Tumors

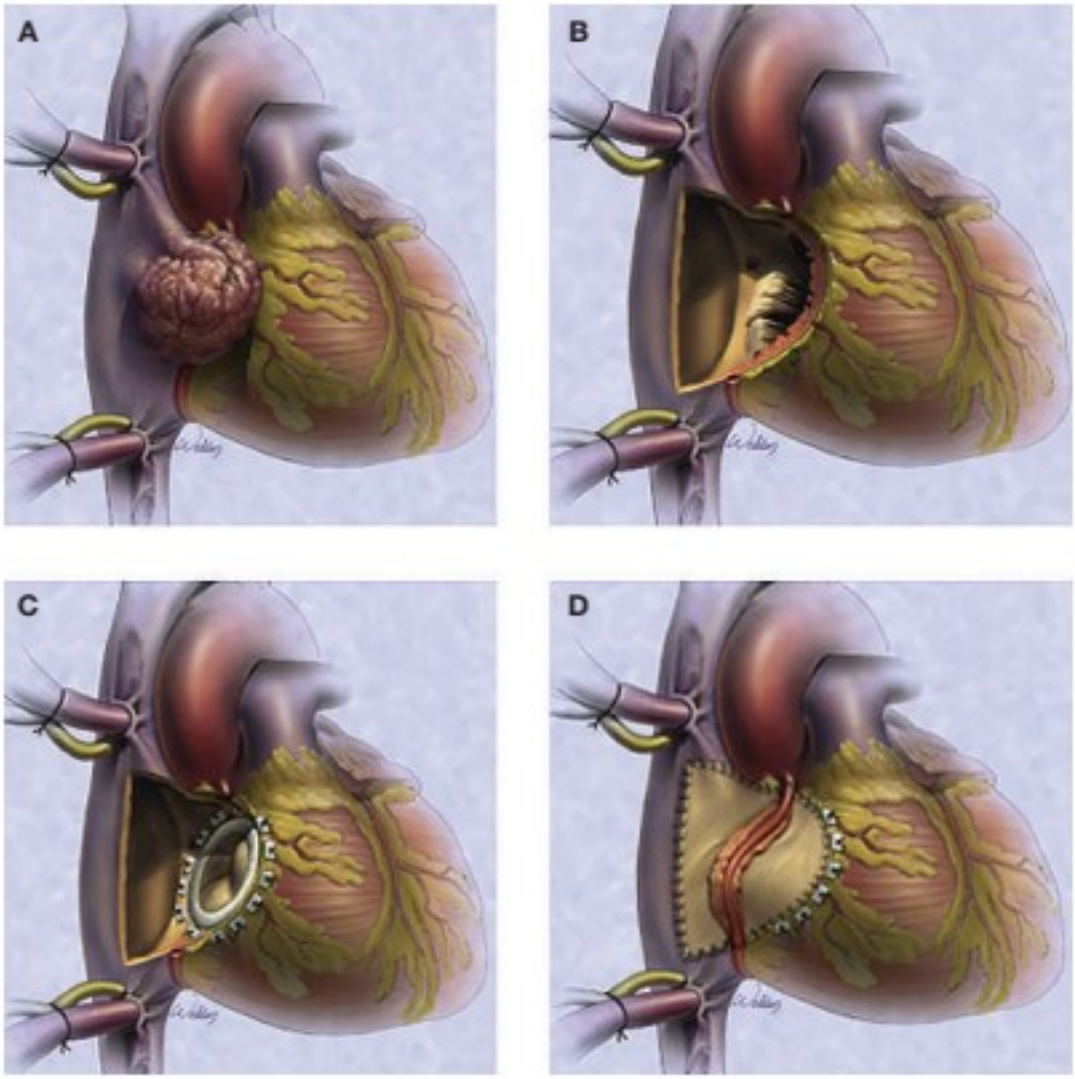
Malignant cardiac tumors continue to pose a therapeutic challenge to cardiac surgeons and oncologists because of the technical difficulty involved in extensive cardiac resections and the aggressive biological nature of the tumors. Primary malignant tumors are relatively rare, accounting for up to 25% of all primary cardiac tumors in third level referral centers. They usually affect people aged 30–50 years, and are mainly represented by sarcomas (angiosarcoma, rhabdomyosarcoma, leiomyosarcoma, liposarcoma, osteosarcoma, fibrosarcoma, and malignant fibrous histiocytoma) and lymphomas (49-51). Angiosarcomas are usually located in the right chambers of the heart, whereas other sarcomas affect the left atrium more frequently. Lymphomas with bi-atrial localization have also been reported (68). Malignant tumors have usually a poor prognosis in view of the extensive infiltration of the myocardium, the frequent obstruction of intracardiac flow, and the occurrence of metastases. The decision to resect a primary malignant tumor is based on several variables, including tumor location and size, histology, grade of myocardial infiltration, relationship with the cardiac valves and the fibrous skeleton of the heart, absence of metastatic spread, and potential for a radical excision of the mass. Other more general variables, such as age, overall clinical conditions, frailty, and comorbidities, will also need to be considered to finalize the surgical strategy (68-74). Currently, chemotherapy, radiation therapy, or a combination of both are used as an adjuvant to decrease tumor size and facilitate surgical resection. In this perspective, a multidisciplinary decision-making approach relative to the overall therapeutic management is mandatory. If complete resection is possible, respecting the anatomical and functional integrity of the heart, surgery provides better palliation and can improve survival vs. medical therapy alone (68-74). To overcome the technical challenges of complete resection with accurate cardiac reconstruction, particularly of left-sided tumors with posterior extension, a technique of cardiac explantation, ex vivo tumor resection with cardiac reconstruction, and cardiac reimplantation—cardiac autotransplantation—has been utilized (69,70,75). Surgical outcomes with

cardiac auto-transplantation are excellent in patients who do not require concurrent pneumonectomy (69). In selected cases of right ventricular tumors, a right heart bypass (cavo-pulmonary anastomosis) has also been utilized as a palliation to prolong survival (22). The role of orthotopic cardiac transplantation in the management of locally advanced non-metastatic cardiac tumors appears to be limited. Indeed, it has been shown that about two-thirds of the so treated patients die of local recurrence or distant metastases within a year. Nevertheless, about 25% of the patients managed by orthotopic cardiac transplantation have a mean survival of more than 2 years without recurrent disease (70, 76).

a. Angiosarcoma

These tumors tend to be bulky and aggressively invade adjacent structures, including the great veins, tricuspid valve, right ventricular free wall, interventricular septum, and right coronary artery (77). Obstruction and right-sided heart failure are not uncommon. Pathologic examination of resected specimens demonstrates anastomosing vascular channels lined with typical anaplastic epithelial cells. Unfortunately, most of these tumors have spread by the time of presentation, usually to the lung, liver, and brain (78). Without resection, 90% of the patients are dead within 9 to 12 months of diagnosis despite radiation or chemotherapy (78). We have seen carefully selected patients without evidence of spread on metastatic evaluation who have undergone complete surgical resection with subsequent chemotherapy (*Figure 12.12*). Surgical resection may include the right atrium. In addition, right coronary bypass and even tricuspid valve repair or replacement may be undertaken. We have had no hospital mortality in this small group, and the main problem remains metastasis rather than recurrence at the local site.

Figure 12.12: *(A) Right atrial angiosarcoma involving right coronary artery and tricuspid valve. (B) Excision of tumor with right coronary artery and tricuspid valve. (C) Tricuspid valve replaced. (D) Completed repair using bovine pericardium and perfomed bypass graft. (Copyright 2002, Baylor College of Medicine.). From: Walkes JC et al., Cardiac surgery in the adult, 2008.*



b. Rabdomiosarcoma

The tumors are aggressive and may invade pericardium. Surgical excision of small tumors may be rational, but local and distant metastases and poor response to radiation or chemotherapy limit survival to less than 12 months in most of patients (79,80).

12.5 Other Sarcomas and Mesenchymal-Origin Tumors

Myosarcoma, liposarcoma, osteosarcoma, chondro-myxosarcoma, plasmacytoma, and carcinosarcoma arising from the heart all have been reported, but by the time diagnosis is made, only palliative therapy usually can be offered, and surgery is indicated only occasionally (81,82). Regardless of therapy, it is unusual for patients with these diagnoses to survive more than a year.

a. Lymphomas

Lymphomas may arise primarily from the heart, although this is rare (83). Most of these tumors respond to radiation and chemotherapy. Even when complete resection is not possible, and incomplete resection is performed to relieve acute obstructive systems, radiation and chemotherapy have allowed for up to 3-year survival in selected patients.

12.6 Secondary Metastatic Tumors

Metastatic cardiac tumors are far more frequent (approximately from 20-fold) than primary tumors of the heart. Although almost every type of malignant tumor has the potential to reach the heart, they usually arise from melanomas, lung, breast, and renal cancer, as well as lymphomas. Metastases may originate from blood dissemination via coronary arteries (melanoma, sarcoma, bronchogenic carcinoma) or lymphatic channels of cancer cells, direct extension via adjacent tissues (lung, breast, esophageal, and thymic tumors), or propagation via the superior or the inferior vena cava to the right atrium (liver, kidney tumors). The pericardium is most often affected by direct extension of thoracic cancer, resulting in pericardial effusion which may contain masses comprising either cancer cells or blood clots and fibrin. The myocardium is the target of hematologous and/or retrograde lymphatic metastasis. Surgical therapy is limited to relief of

recurrent pericardial effusions or, occasionally, cardiac tamponade. In most instances, these patients have widespread disease with limited life expectancies. Surgical therapy is directed at providing symptomatic palliation with minimal patient discomfort and hospital stay. This is most readily accomplished via subxiphoid pericardiotomy, which can be accomplished under local anesthesia if necessary with reliable relief of symptoms, a recurrence rate of about 3%, and little mortality (83). Alternatively, a large pericardial window in the left pleural space can be created using thoracoscopy (84), but we would recommend this only under unusual circumstances. This can be accomplished with minimal patient discomfort but does require general anesthesia with single-lung ventilation and may be poorly tolerated by patients with hemodynamic deterioration secondary to large effusions.

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CHAPTER 13

MEDICAL THERAPY AND CARDIOTOXICITY

Malignant cardiac tumors are usually sarcomas or Non-Hodgkin Lymphomas (NHL). The treatment of NHL is based on chemotherapy (CT), and surgery is commonly used as a rescue therapy to treat severe hemodynamic impairment by a large mass. Although sarcomas are very rare and large institutions usually see roughly one patient/year or less, it impossible to plan randomized studies to assess the best treatment approach (1-5). Cardiac sarcomas are a small subgroup of the more frequent sarcomas of other sites (they represent roughly 1/100 of all sarcomas), and in most cases they pertain to the soft tissue sarcomas (STS) group. Therefore, the basic therapeutic approach should be based on extrapolation of data from the most frequent tumor sites, including STS of the extremities and trunk (2, 5-7). In fact, cardiac sarcomas are at higher risk of recurrence and they have a worse prognosis compared to STS of other more frequent anatomical sites, including extremities, superficial trunk, retroperitoneum, and head and neck (7). The standard treatment for localized STS consists of adequate surgery with extensive resection followed by postoperative radiation therapy (RT) in most cases. Preoperative RT may be an option for large tumors or more critical tumor sites where surgery may not be radical (8,9). The role of adjuvant CT has not been yet defined so far, but clinical practice guidelines include it as an option in high- risk patients (9,10). The particular location of cardiac sarcomas makes both surgery with curative intent and the use of RT particularly challenging. While CT is mandatory in metastatic and/or locally advanced, unresectable disease, its use has been proposed for some critical locations, such as right heart/pulmonary artery sarcomas, attempting to increase the number of resections with negative margins (11,12).

Therefore, a multimodality approach, including CT and/or RT before or after surgery, has been used by several authors even for localized, non-metastatic tumors, and it seems to be effective in prolonging both time to relapse and survival in some selected studies. The outcome data reported in different papers are conflicting for some reasons: a wide variety of tumor presentations (metastatic vs. non-metastatic, high-grade vs. low or intermediate grade, right vs. left heart, surgery limited to the heart or including the lung); a non-standard surgical approach; and, in most studies, a multimodality therapy is limited to patients with incomplete resection or metastatic disease (11, 13-25). Overall, when comparing studies with a multimodality approach, regardless of the surgical outcome, and historical studies with CT used in some subgroups of patients only, there seems to be a favorable trend for the multi-modality approach (21-25).

The most common regimen for soft tissue sarcoma treatment is combined doxorubicin and ifosfamide but anthracycline chemotherapy is both cardiotoxic and a radiation sensitizer (26). Nevertheless, an initial large meta-analysis of adjuvant chemotherapy trials has shown no survival benefit of adjuvant chemotherapy for adult soft tissue sarcomas (27).

Planning the best treatment strategies for primary cardiac sarcoma will need improved understanding of natural history and prognostic factors of this very rare disease. Thus, patients should be referred to treatment in specialised centres, and multicentre data poolong should be coordinated through intergroup reseaech organisations.

Cardiotoxicity

Most of the treatments have a considerable risk of cardiac toxicity, but this risk should be balanced with the risk of tumor progression. Since the survival is usually limited to few years, the main concern is to prevent short- and medium-term toxicity. CT adverse effects may be prevented with careful dosage of drugs, cardioprotective agents, and strict monitoring of cardiac function. Short- and medium-term cardiac toxicity of RT may be limited using modern radiation techniques. A

number of new targeted therapies are under evaluation and will hopefully improve the outcome of this severe pathology.

Coronary artery disease, valvular heart disease, and constrictive pericarditis are the typical chronic side effects affecting long-term survivors: they become clinically evident usually 10 years after the treatment, with increasing incidence at longer follow-up (28). The first acute effect of irradiation is a pro-inflammatory effect, with endothelial damage of medium-large vessels and microvessels, pericarditis, and myocarditis (28-30). Pericardium is the most frequently affected site: acute pericarditis is associated with edematous swelling of the pericardial layers: it may be present in a painless effusive form with spontaneous recovery, or as an acute fibrinous pericarditis that can be cured with Nonsteroidal Anti-inflammatory Drugs. In both cases, pericardial effusion is usually mild to moderate, and in 80% of cases there are no reliquates, while in the remaining 20% the disease evolves toward a constrictive pericarditis (31). The microvessel damage is followed by a persistent decrease in capillary density and eventually leads to chronic myocardial ischemia and degeneration; an impairment in myocardial perfusion may be observed in the first months after RT, even if the increased risk of clinically evident RT-linked ischemic heart disease becomes statistically significant only after 10 years (30, 31-34).

The cardiotoxicity of CT are various and depending of treatment used. In fact, it has been studied for decade as damage site effect control of Doxorubicin (DOX) and other anthracyclines (ANTHRA). These damage of myocytes is both iron-dependent and iron-independent (35-37). Ultrastructural early alteration in damaged myocytes consists of distension of sarcoplasmic reticulum to form sarcoplasmic vacuoles, followed by myofibrillar lysis and focal proliferation of sarcoplasmic reticulum, disruption of myofibrils, atrophy, and necrosis; interstitial edema and eventually fibrosis are observed in more severe forms. Myocardial damage has been reported as most severe in the left ventricle (LV) and in the ventricular septum, intermediate in the right ventricle and the left atrium, and at least in the right atrium (38). Each single dose of DOX causes an irreversible cardiac damage; for this reason the cardiotoxicity is cumulative, even for CT given

many years apart. The final effect is a diastolic and systolic left ventricular dysfunction and, in the most advanced stages, a congestive heart failure (CHF).

The main reported toxicities of ifosfamide (IFO) are nephrotoxicity and neurotoxicity. From the cardiac point of view it has been usually considered safe, but cardiac toxicity in high-dose (>10 g/m^2) treated patients has been reported, and it is significant (>10%) when using >15 g/m^2 (39-42). Taxane cardiotoxicity is mostly evident as a self-limiting supraventricular arrhythmias (atrial fibrillation, sinus bradycardia), but they may also increase DOX (much less EpiDOX) toxicity, altering ANHTRA pharmacokinetics and possibly promoting the formation of toxic metabolites (35,36,41). Finally, Vascular Endothelial Growth Factor Blocking Agents and Tyrosine Kinase Inhibitors (VEGF block) (by the monoclonal antibody Bevacizumab and the tyrosine kinase inhibitors (TKI) Sunitinib and Sorafenib) causes hypertension (mainly by reducing the nitric oxide release by the endothelial cells, by interfering with renal physiology, and by increasing the vascular resistance), thromboembolism, and hemorrhages (43-45).

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CHAPTER 14

FUTURE DIRECTIONS

The clinical outcome of patients with a primary cardiac tumor depends heavily on early detection and prompt, appropriate treatment. It is a frequent phenomenon that cardiac tumors are discovered only after a patient experiences a period characterized by a confusing constellation of symptoms that are ultimately connected to abnormal findings on an image suggestive of a cardiac tumor. As a result, an advanced stage of disease is already commonly present at the time of diagnosis. Over the last few years the increasing use of imaging modalities (e.g., echocardiography, MRI, and CT) has led to an increasing number of incidental findings of primary cardiac tumor. However, current imaging techniques can accurately differentiate tumors from other causes of masses seen on imaging only slightly more than 50% of the time. It is hoped that with improvement in echocardiography, CT, and MRI techniques, all cardiac tumors would be identified with a high degree of certainty. There is no non-invasive technique that can identify whether the tumor is benign or malignant, and therefore a pathologic sample is needed in all cases. Improvement in surgical technique has led to minimally invasive approaches, but this still entails general anesthesia and a surgical incision and is the source of major stress for a patient. Continued refinement of surgical tools and approaches will lead to less morbidity and mortality (1). Transvenous biopsy of the cardiac mass for pathologic confirmation (under echocardiographic guidance) is done at some centers. Refinement of this technique will enable better sampling in the future. In some centers, PET is routinely used to evaluate for metastatic disease. Currently, no blood tests are available that would point to metastasis.

Better noninvasive imaging of tumor extension is needed because at present only a minority of patients with right-sided heart sarcoma have a pathologically negative margin after resection, and the use of neoadjuvant chemotherapy in selected cases may provide better results, but outcomes

need to be reported in a disciplined manner (2). All patients should be managed by a multidisciplinary team that includes medical oncologists, radiation oncologists, cardiologists, and cardiac surgeons. Over next few years it is hoped that better targeted therapy will be developed that will inhibit or arrest the malignant proliferating endothelial cells. Cardiac autotransplantation, which was originally performed by Dr. Cooley in 1984 (3), is now a standard practice for complex cases in some centers. With further improvement in surgical techniques, chemotherapy, and radiation therapy, the overall prognosis of patients with cardiac tumors will continue to improve.

14.1 References

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PART II

EPIDEMIOLOGY AND SURGICAL PATHOLOGY OF PRIMARY CARDIAC TUMORS IN VENETO REGION OF ITALY (2005-2016)

THE AIM OF THE STUDY

The study has been divided into two phases:

1. The first one consisted in the creation of a Registry of Primary Cardiac Tumors in the Veneto Region, involving all Cardiac Surgery Centers and Pathological Anatomy Units, by performing an epidemiological analysis.

2. The second phase aimed to analyze the short and long-term results of the surgical treatment of cardiac tumor using a retrospective analysis over a range of 12 years of experience in three Cardiac Surgery Centers of the Veneto Region. The results will be analyzed in terms of short and long term mortality, tumor recurrence rates, re-intervention freedom and all preoperative, intraoperative and postoperative variables conditioning the results.

MATERIALS AND METHODS

This study was a multi-center, retrospective study over 12 years (2005-2016). All patients who underwent cardiac surgery due to a primary cardiac tumor confirmed by pathology in the Veneto Region at the Centers for Cardiac Surgery and Pathological Anatomy of Mestre, Treviso, Mirano, Padova, Vicenza and Verona were included for analysis. All eligible records from the selected hospitals were reviewed: (1) demographic characteristics and possible risk factors at the time of diagnosis, including age, gender, height and weight, occupation, family history of tumor (whether malignant or benign, occurred on parents or siblings), smoking habit; (2) clinical features, including primary tumor sites; (3) results of imaging tests, including ultrasound, CT, MRI; (4) use of currently available treatment approaches, including surgery, chemotherapy, biological therapy and target therapy; (5) pathological characteristics, including tumor size, infiltration, mitosis rate, Ki-67 labeling index.

The cardiac surgery and pathological anatomy databases were used to identify the patients who were diagnosed with primary cardiac tumors, and then the detailed medical records of these patients were reviewed with special attention to confirm the presence, location and histological type of the tumors.

Surgical treatment was performed through extracorporeal-circulation, aortic clamping and cardioplegic arrest by anterograde or retrograde with cold blood or crystalloid cardioplegia. After the removal of the heart tumor by the anchorage site and the size was reconstituted with the base of the plant with or without the use of an autologous pericardial patch, equine or bovine pericardium patches or patches of synthetic material (Dacron). Mininvasive approach was performed with Heartport Access system and video-assisted thoracoscopic surgery.

Pathological materials from all patients studied were available for gross and histological examinations. Specimens were fixed in formalin, routinely processed for light microscopy and

stained with hematoxylin-eosin, Alcian-periodic acid-Schif (PAS), Heidenhaim trichrome and Weigert van Gieson. When required, transmission electron microscopy and immunohistochemistry studies were performed to confirm the histological diagnosis.

Follow-up information was obtained from subsequent medical examination or phone-call.

Statistical Analysis

To evaluate the effects of various clinical variables on postoperative death and complications/ adverse events (such as cardiac/non–cardiac-related death, reoperation, recurrence of cardiac/noncardiac tumor) at follow-up, we applied the following statistical tests.

Log-rank test and Fisher's exact test were used to test effect of clinical variables on survival. Because the precise chronology of adverse events was not always known, we included all complications and adverse events occurring during follow-up.

Finally, McNemar test was used to determine a significant difference of 2 major clinical variables (NYHA class and Ejection fraction) before and after surgical repair, early and late. Survival curves were constructed with Kaplan-Meier estimates. Probability values <0.05 were considered statistically significant. Analyses were performed using SAS System, version 9.2.

RESULTS 1

Epidemiological and Surgical Pathology of findings of the whole cohort

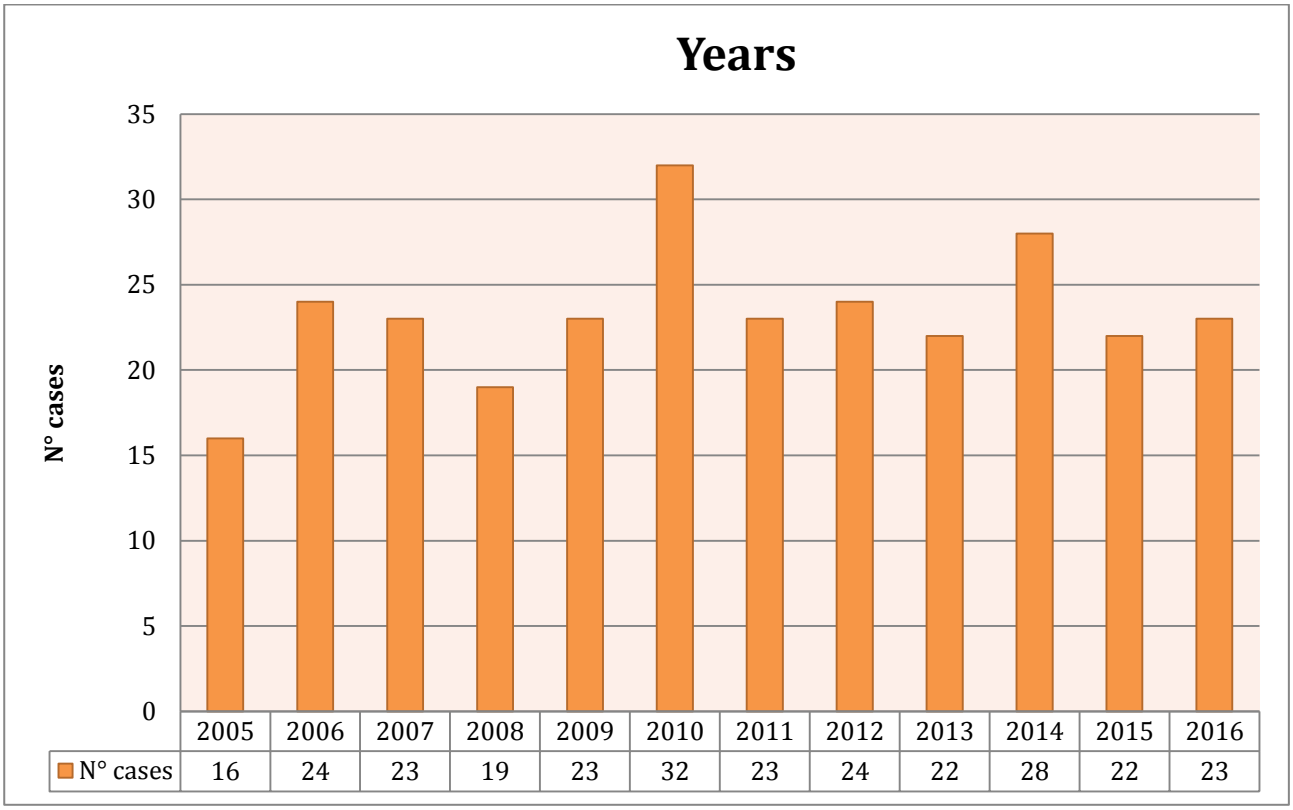
In the Registry of Primary Cardiac Tumors in the Veneto Region, the study population included 279 patients, 254 patients (91.03%) were affected by benign primitive cardiac tumors and 25 patients (8.97%) by malignant cardiac tumors. The Table 1 and Figure 1 list the number of tumors and case distribution per year in the 6 Cardiac Surgery Centers (*Table 1, Figure 1*).

Table1 *Frequence of surgically resected primary cardiac tumors in the Veneto Region Population (2005-2016).*

Cardiac Surgery Units in Veneto Region	Benign Tumors 2005-2016	Malignant Tumors 2005-2016	Total
Padova	79	6	85
Mestre	33	2	35
Mirano	10	1	11
Treviso	30	2	32
Verona	50	8	58
Vicenza	52	6	58
Total	254 (91.03%)	25 (8.97%)	279 (100%)

According to the Census Data of Veneto Region, the median of resident population was 4.876.601 in the time interval 2005-2016. The incidence of primary cardiac tumors in Veneto Region was constant every years and the average incidence in the general population is 0.47% (from 0,33% to 0,64%), 47 cases per 100.000 in men and women.

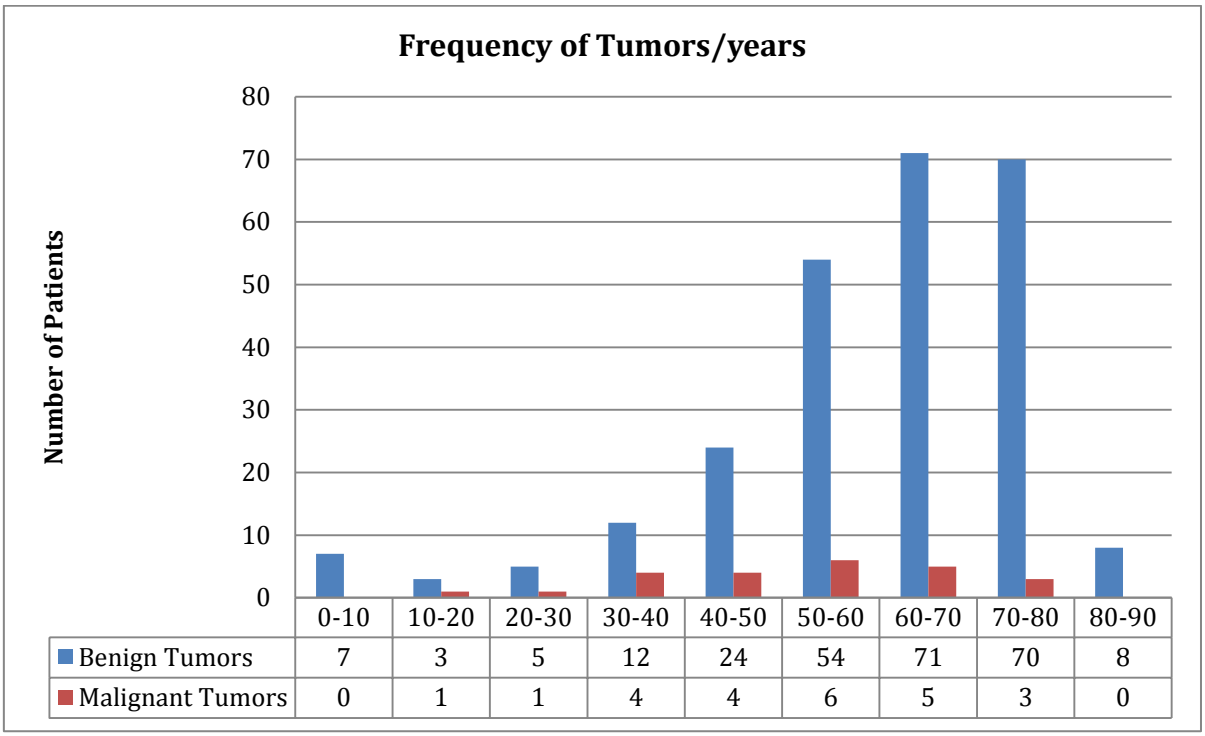
Figure 1 *Number of cases per year of surgically resected primary cardiac tumors in the Veneto Region (2005-2016).*



The mean age of 59.8±16.8 years (ranging from 1 month to 83 years), 155 female (55.6%). Our series showed that frequency of primary cardiac tumors was quite different among age groups with the highest in the age group 60–70 years (n=75, 26,88%). In this age range there were 71 benign tumors and only 5 were malignant. Cardiac myxoma has a peak of incidence between the fifth and sixth decades of life. Rhabdomyoma and fibroma are the most common benign cardiac tumors in children: 2 rhabdomyoma where only in age group 0-10 years, and the ages were for

both 4 months; there are only one case fibroma in the same age group and the age was 2 years old (*Figure 2)*.

Figure 2 *Distribution of Primary Cardiac Tumors in Veneto Region by Age Groups (2005-2016).*



	0-10	10-20	20-30	30-40	40-50	50-60	60-70	70-80	80-90
Benign Tumors	7	3	5	12	24	54	71	70	8
Malignant Tumors	0	1	1	4	4	6	5	3	0

The majority of primary cardiac tumors were benign, with the most common being myxoma (n= 178, 70,08%). The remaining benign tumors included papillary fibroelastoma (n= 48, 18,90%), lipoma (n=8, 3,15%), hemangioma (n=7, 2,76), pericardial cyst (n=5, 1,97%), inflammatory miofibroblastic tumor (n=3, 1,18%), rhabdomyoma (n=2, 0,79%), fibroma (n=1, 0,39%) and other benign tumors (n=2, 0,79%)(*Figure 3 and Table 2).*

Figure 3 *Benign Cardiac Tumors in Veneto Population.*

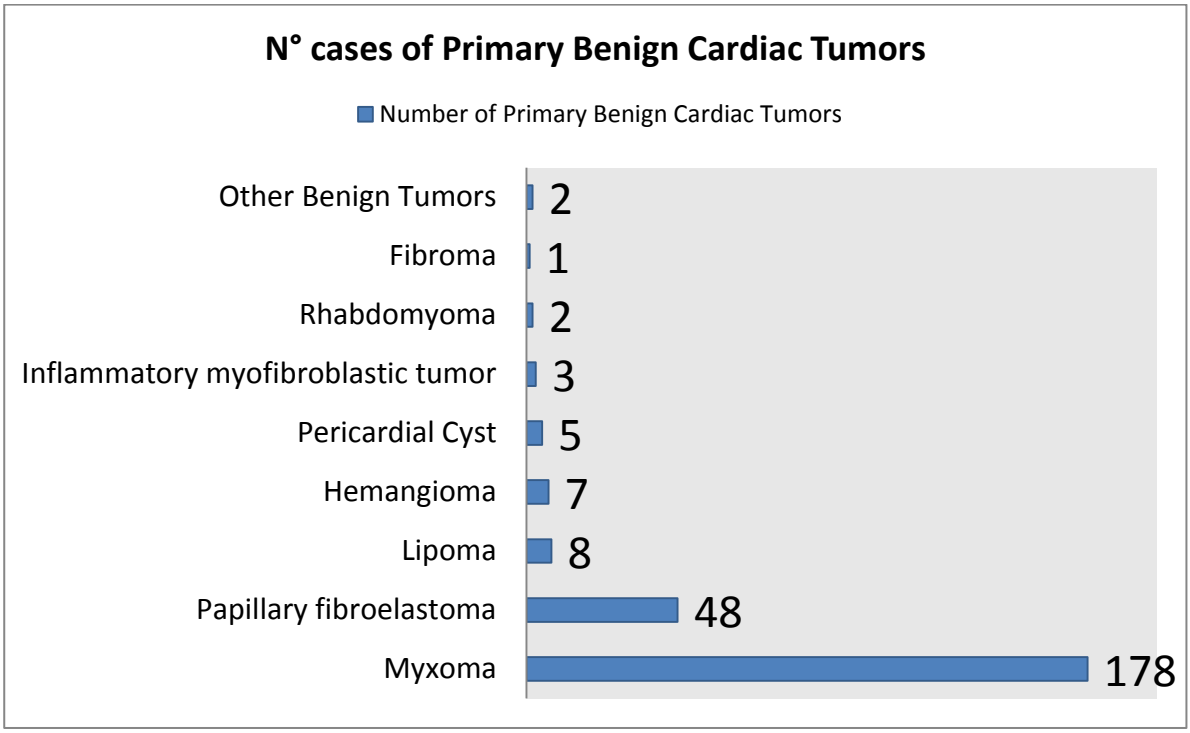
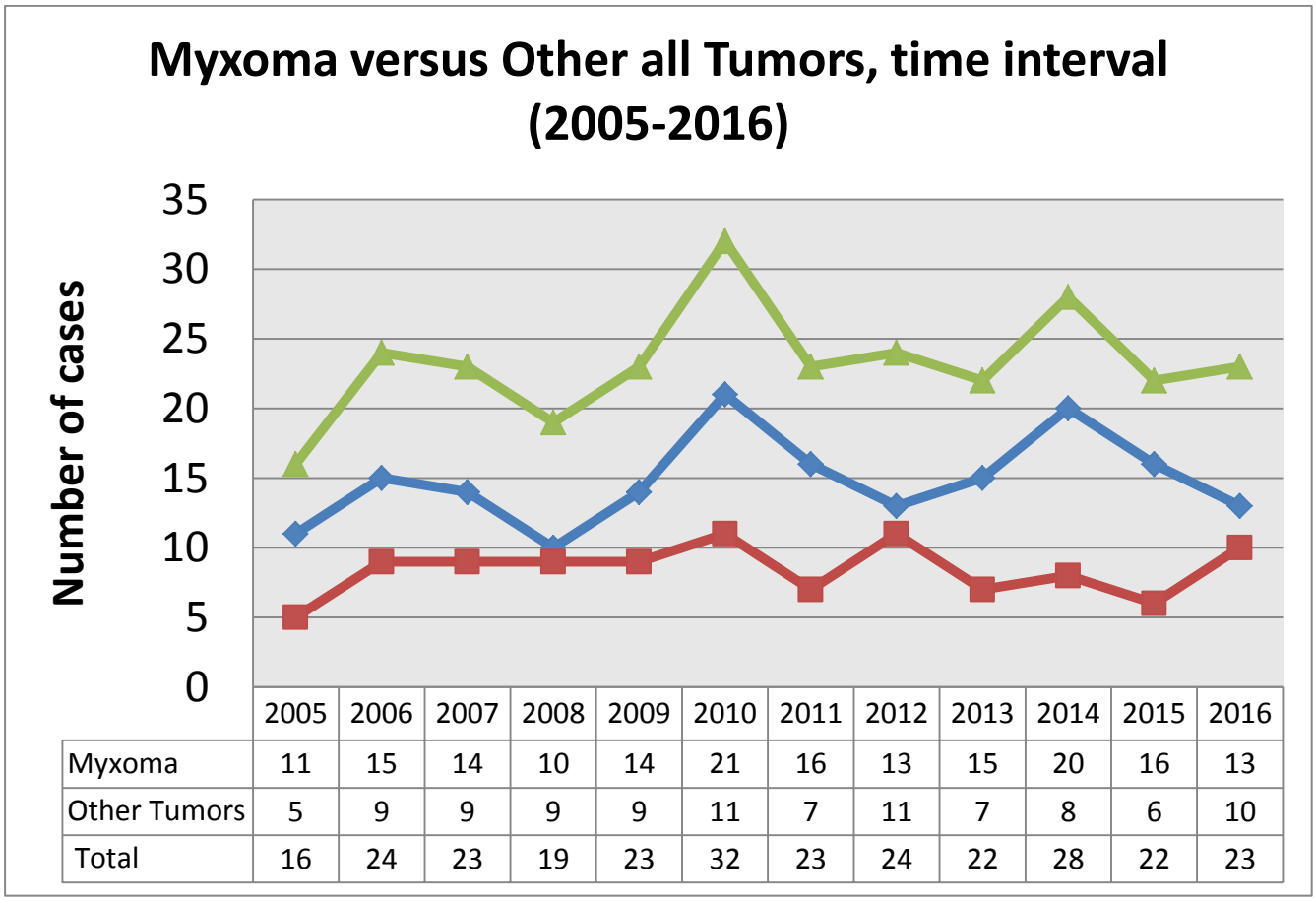


Table 2 *Benign Cardiac Tumors in Veneto Population.*

	Myxoma	Papillary Fibroelastoma	Lipoma	Hemangioma	Pericardial Cyst	Inflammatory Myofibroblastic	Fibroma	Leiomyoma	Rhabdomyoma	TOTN %
Padova	46	15	3	7	4	1	1	0	2	79 (31,1 %)
Mestre	25	6	2	0	0	0	0	0	0	33 (13,0 %)
Mirano	8	2	0	0	0	0	0	0	0	10 (3,9 %)
Treviso	26	2	1	0	0	1	0	0	0	30 (11,8 %)
Verona	41	5	2	0	1	1	0	0	0	50 (19,7 %)
Vicenza	32	18	0	0	0	0	0	1	0	52 (20,5 %)
	178 (70,08 %)	48 (18,90 %)	8 (3,15%)	7 2,76 %)	5 (1,97 %)	3 (1,18%)	1 (0,39%)	2 (0,79%)	2 (0,79%)	254 (100 %)

Cardiac myxoma is the most frequent primary cardiac tumor and have a costant frequency in the time interval considered compared with all other tumors *(Figure 4).*

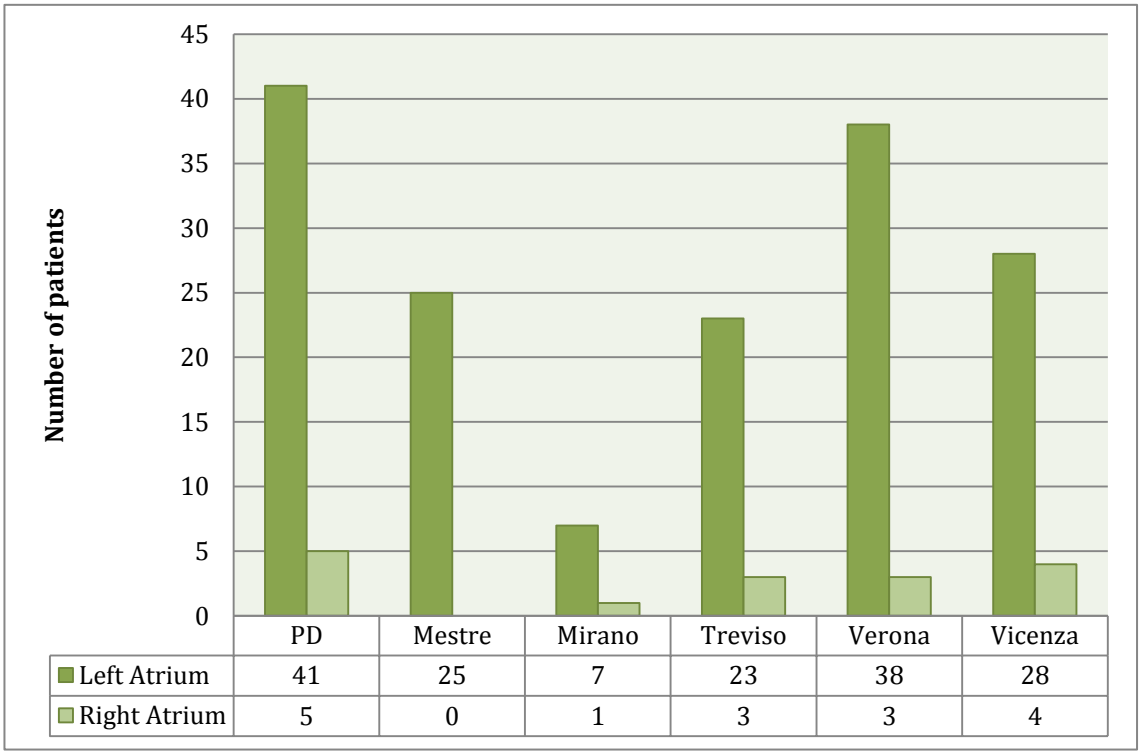
Figure 4 *Frequency of Myxoma and Other primary benign tumors in Veneto Region Population (2005-2016).*



	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Myxoma	11	15	14	10	14	21	16	13	15	20	16	13
Other Tumors	5	9	9	9	9	11	7	11	7	8	6	10
Total	16	24	23	19	23	32	23	24	22	28	22	23

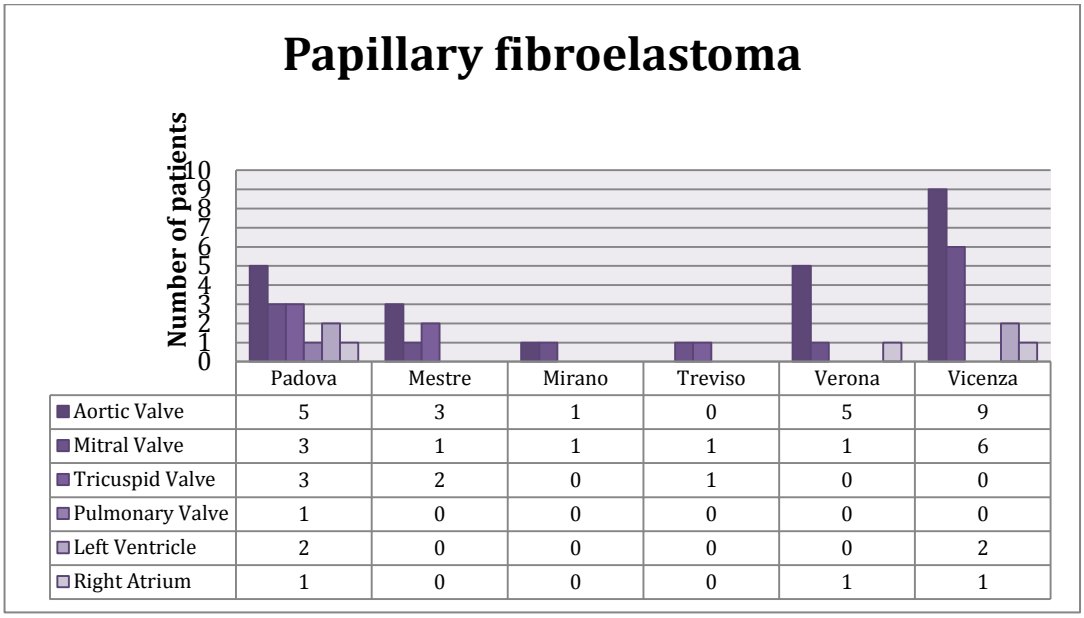
The majority were female (103, 57,86%), the age range was 5-83 years (mean 62,06±14,4). Myxoma is the paradigm of intra-cavitary cardiac tumour, mostly arising in the left atrium followed by the right atrium, and only occasionally the ventricles. In our experience, myxoma was located in the left atrium in 91% of cases (162/178) and in the right atrium in 9% (*Figure 5*).

Figure 5 *Location of atrial myxoma.*



Papillary fibroelastoma is the second primary cardiac tumour in our series (N=48, 18,9%). All of the 48 patients have been surgically resected, 24 female, age ranging from 28 to 83 years, mean 62,5±14,9 years. The most common location was the valvular endocardium, 83.3% arising in the left heart, in particular aortic valve (n=23, 47.9%), mitral valve (n=13, 27.1%); tricuspid valve (n=6, 12.5%) and pulmonary valve (n=1, 2.1%) were less frequently involved. Seven patients have mural endocardium location (4 lefts ventricle, 3 right atrium)(*Figure 6*).

Figure 6 *Location of Papillary fibroelastoma.*



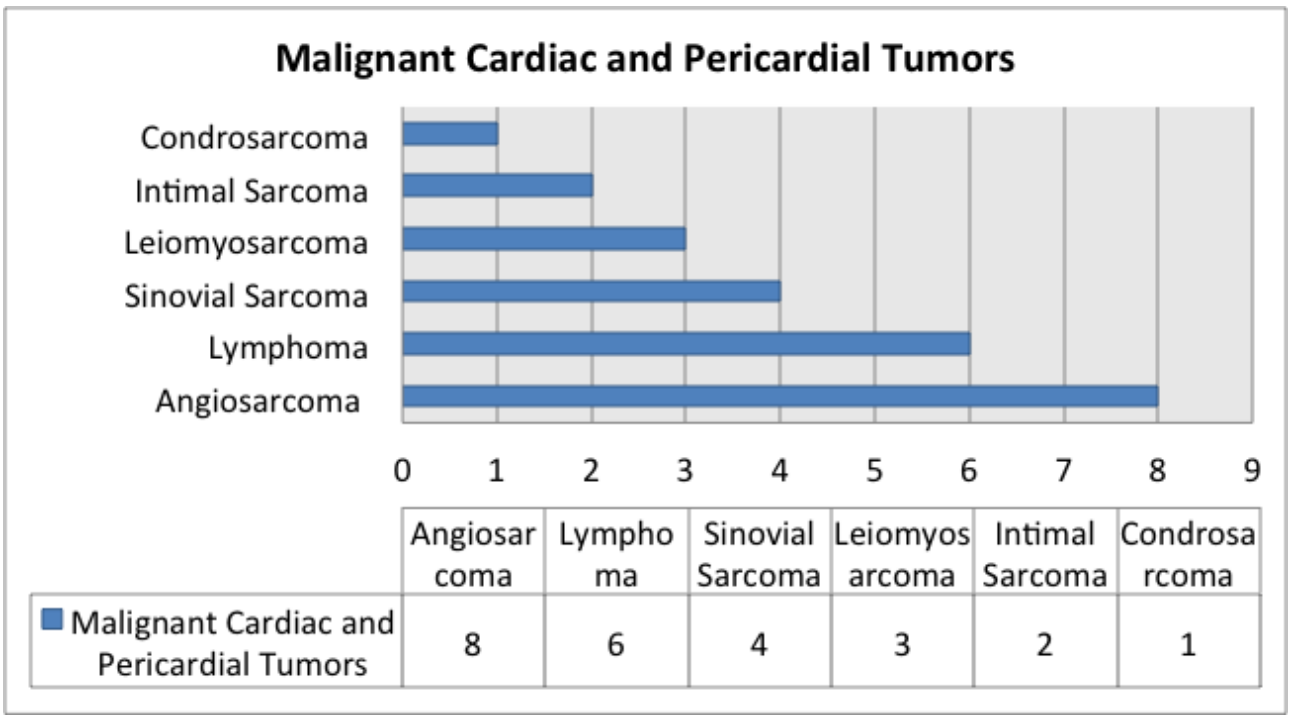
	Padova	Mestre	Mirano	Treviso	Verona	Vicenza
Aortic Valve	5	3	1	0	5	9
Mitral Valve	3	1	1	1	1	6
Tricuspid Valve	3	2	0	1	0	0
Pulmonary Valve	1	0	0	0	0	0
Left Ventricle	2	0	0	0	0	2
Right Atrium	1	0	0	0	1	1

Primary malignant cardiac tumours are very rare, representing nearly 10% of all primary cardiac neoplasms. The population consists of 25 patients, 13 male and 12 female. Primary cardiac sarcomas can occur at any age, but are more frequently diagnosed between the third and fifth decades, and equally in men and women. The age ranging was 18-80 years, mean 52,52±16,1. The most prevalent histotype was angiosarcoma (n=8, 32.5%) followed by primary cardiac lymphoma (n=6, 24%), leiomyosarcoma (n=3, 12%) and synovial sarcoma (n=4, 16%) represented the main malignant primary cardiac tumours in our population, as shown in *Table 3* and *Figure 7*. Tumor location was the left atrium in four (one leiomyosarcoma, one intimal sarcoma and two synovial sarcoma); the right atrium in six (five angiosarcoma and one B cell lymphoma); the bi-atrium in five (one angiosarcoma, one B cell lymphoma, one synovial sarcoma and two leiomyosarcoma); the right ventricle in four (three lymphoma, one intimal sarcoma); the right heart in two (angiosarcoma); and the pericardium in two (one myofibroblastic malignant tumor, one condrosarcoma); finally in one synovial sarcoma and in one lymphoma cardiac involvement was diffuse.

Table 3 *Surgically Resected Primary Malignant Cardiac Tumors in Veneto Population.*

	Angiosarcoma	Cardiac Lymphoma	Leiomyosarcoma	Synovial Sarcoma	Intimal Sarcoma	Condrosarcoma	Myofibroblastic Malignant tumor	TOT N%
Padova	2	1	1	1	0	0	1	6 (24,0%)
Mestre	1	0	0	1	0	0	0	2 (8,0%)
Mirano	0	1	0	0	0	0	0	1 (4,0%)
Treviso	0	0	0	1	1	0	0	2 (8%)
Verona	5	3	0	0	0	0	0	8 (32,0%)
Vicenza	0	1	2	1	1	1	0	6 (24,0%)
	8 (32.0%)	6 (24.0%)	3 (12%)	4 (16%)	2 (8%)	1 (4.0%)	1 (4.0%)	25 (100%)

Figure 7 *Surgically Resected Primary Malignant Cardiac Tumors in Veneto Population.*

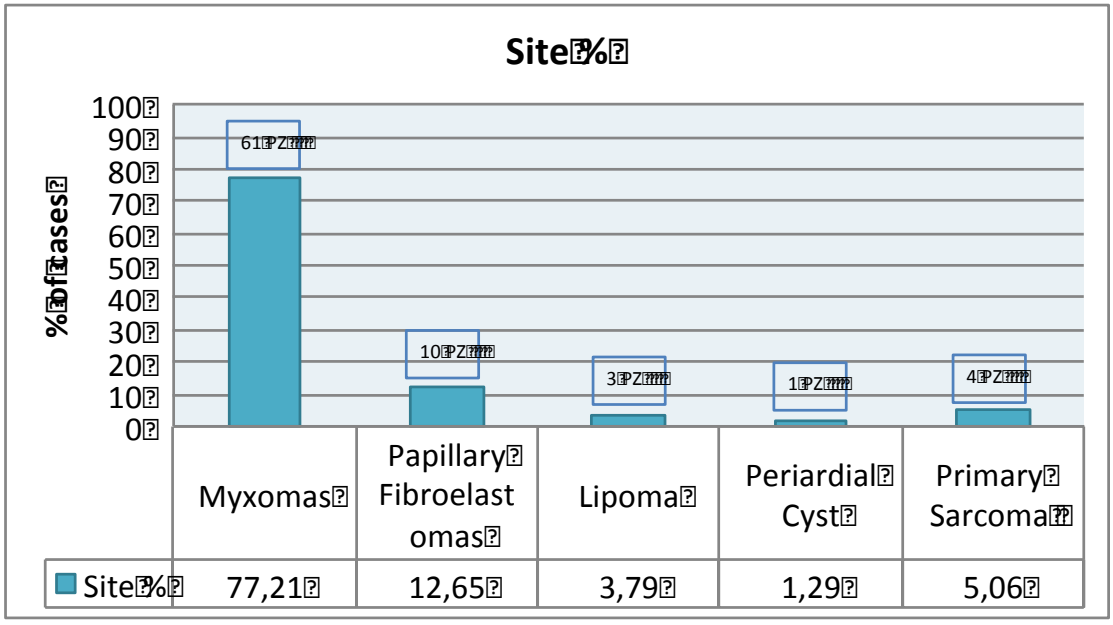


RESULTS 2

Clinical, Surgical and Follow-up Data of the subgroup cohort

From January 01, 2005 to December 2016, the subgroup of 79 consecutive patients underwent cardiac surgery for primary cardiac tumors at three Cardiac Surgery Units (Mestre, Mirano, Treviso) of Veneto Region. Of the 79 operated patients, 74 (93.7%) had a primary benign tumor and 4 (6.3%) a malignant tumor. Benign tumors included myxomas (n=61, 77.21%), papillary fibroelastoma (n=10, 12.65%), lipomas (n=3, 3.79%), pericardial cyst (n=1, 1.29%). Malignant tumors (n=4, 5.06%) included angiosarcoma (n=1, 25%), synovial sarcoma (n=2, 50%), intimal sarcoma (n=1, 25%), primary cardiac lymphoma (n=1, 25%) *(Figure 8)*. 68 patients (86%) were operated by standard sternotomy and 11 patients (14%) with mininvasive approach including 6 with Heartport Access system and video-assisted thoracoscopic surgery. 16 patients (20%) underwent an associated procedure (coronary artery bypass grafting, aortic valce replacement, mitral valve repair or replacement and tricuspid valve repair).

Figure 8 *Frequency of the primary cardiac tumors in the surgical series, three Cardiac Surgery Units (Mestre, Mirano, Treviso) of Veneto Region.*



Overall, the mean age at tumor diagnosis was 63.3±15.2 years and females were affected in 51.9%. The most common presenting symptoms were dyspnea (n=19, 24.1%), thromboembolic event (n=7, 8.9%), and chest pain (n=23, 29.1%); 11.4% (n=9) of patients presented in New York Heart Association (NYHA class) III/IV. Cardiovascular risk factors included hypertension in 53.2% (n=42), coronary artery disease in 25.3% (n=20). Clinical data of patients are shown in *Table 4A*. In survival analysis, none of the clinical variables considered was statistically significant. Moreover, comparing myxomas and other primary benign cardiac tumors, no significant difference was found in cardiovascular risk factors, apart from a higher incidence of hypertension in patients affected by myxomas. All of the patients were diagnosed with echocardiography and angiography, cardiac MRI was performed in 6 patients (7.6%).

Tumor and hemodynamic characteristics are shown in *Table 5A* and 5*B*. Associated valve diseases did not correlate neither with the development of a cardiac tumor nor with the outcome of the patients who underwent tumor resection.

There was significant correlation between tumor histotype and location in the heart. Specifically, left (n=59, 74,7%) and right atrial tumors (n=7, 8,9%) were primarily myxomas, whereas valvular tumors were predominantly papillary fibroelastomas. There was a relatively equal distribution of the various histological subtypes of ventricular tumors; however, cardiac fibromas occurred exclusively in the ventricle. Additionally, primary tumors of the great arteries were malignant. There was a higher incidence of mitral regurgitation in patients with left atrial and aortic valve tumors.

Table 4A *Comparison of the clinical features in relation of survival of the 3 Center Surgical series.*

Clinical features (n=79)	P-Value	Total (N=79)	Death (N=9)	Alive (N=70)
Age at Surgey (Mean ± SD (N))	0,52	63.3 ± 15.2 (N=79)	68.1 ± 6.6 (N=9)	62.6 ± 15.9 (N=70)
Age (Median (min-max))		67.0 (10.0-83.0)	70.0 (57.0-77.0)	66.5 (10.0-83.0)
Sex				
Male	0,3	38 (48.1%)	6 (66.7%)	32 (45.7%)
Female		41 (51.9%)	3 (33.3%)	38 (54.3%)
Risk factors				
Hypertension	0,49	42 (53.2%)	6 (66.7%)	36 (51.4%)
Coronary artery disease	1,00	20 (25.3%)	2 (22.2%)	18 (25.7%)
Preoperative symptoms				
Asymptomatic	0,64	13 (16.5%)	2 (22.2%)	11 (15.7%)
New York Heart Association classification (NYHA class)	0,92			
I		13 (16.5%)	2 (22.2%)	11 (15.7%)
II		21 (26.6%)	2 (22.2%)	19 (27.1%)
III		8 (10.1%)	1 (11.1%)	7 (10.0%)
IV		1 (1.3%)	0 (0.0%)	1 (1.4%)
Syncope	0,31	3 (3.8%)	1 (11.1%)	2 (2.9%)
Chest pain	0,44	23 (29.1%)	4 (44.4%)	19 (27.1%)
Cerebral Events	1,00	5 (6.7%)	0 (0.0%)	5 (7.6%)
Previous Cancer	1,00	67 (100.0%)	5 (100.0%)	62 (100.0%)
Presenting Symptoms	0,38			
Incidental		19 (24.1%)	4 (44.4%)	15 (21.4%)
Dyspnea		19 (24.1%)	1 (11.1%)	18 (25.7%)
Angor		7 (8.9%)	1 (11.1%)	6 (8.6%)
Lipothymia		2 (2.5%)	1 (11.1%)	1 (1.4%)
Arrhythmia		8 (10.1%)	0 (0.0%)	8 (11.4%)
Barkin Cough		1 (1.3%)	0 (0.0%)	1 (1.4%)
Thromboembolism		7 (8.9%)	0 (0.0%)	7 (10.0%)
Dyspnea and angor		11 (13.9%)	2 (22.2%)	9 (12.9%)
Pulmonary Edema		5 (6.3%)	0 (0.0%)	5 (7.1%)

Table 4B *Comparison of the clinical features of patients of the 3 Center surgical series affected by myxomas vs patients affected by other benign primary cardiac tumors.*

Clinical features (N=75)	P-Value	Total (N=75)	Myxoma (N=61)	Other Benign Tumors (N=14)
Age at Surgery (Mean ± SD (N))	0.75	63.6 ± 15.5 (N=75)	64.4 ± 13.9 (N=61)	60.2 ± 21.5 (N=14)
Age (Median (min-max))		69.0 (10.0-83.0)	69.0 (19.0-83.0)	66.5 (10.0-81.0)
Sex	0,25			
Male		38 (50.7%)	33 (54.1%)	5 (35.7%)
Female		37 (49.3%)	28 (45.9%)	9 (64.3%)
Risk factors				
Hypertension	**0,0074**	41 (54.7%)	38 (62.3%)	3 (21.4%)
Coronary artery disease	**0,095**	20 (26.7%)	19 (31.1%)	1 (7.1%)
Preoperative symptoms				
Asymptomatic	0,44	13 (17.3%)	12 (19.7%)	1 (7.1%)
New York Heart Association classification (NYHA class)	0,27			
I		13 (17.3%)	13 (21.3%)	0 (0.0%)
II		20 (26.7%)	16 (26.2%)	4 (28.6%)
III		7 (9.3%)	6 (9.8%)	1 (7.1%)
IV		1 (1.3%)	1 (1.6%)	0 (0.0%)
Syncope	0,47	3 (4.0%)	2 (3.3%)	1 (7.1%)
Chest pain	0,52	21 (28.0%)	16 (26.2%)	5 (35.7%)
Cerebral Events	0,56	4 (5.6%)	3 (5.2%)	1 (7.7%)
Previous Cancer	0,56	64 (100.0%)	53 (100.0%)	11 (100.0%)
Presenting Symptoms	0,83			
Incidental		19 (25.3%)	15 (24.6%)	4 (28.6%)
Dyspnea		18 (24.0%)	16 (26.2%)	2 (14.3%)
Angor		7 (9.3%)	5 (8.2%)	2 (14.3%)
Lipothymia		2 (2.7%)	2 (3.3%)	0 (0.0%)
Arrhythmia		7 (9.3%)	6 (9.8%)	1 (7.1%)
Barkin Cough		1 (1.3%)	1 (1.6%)	0 (0.0%)
Thromboembolism		7 (9.3%)	5 (8.2%)	2 (14.3%)
Dyspnea and angor		9 (12.0%)	8 (13.1%)	1 (7.1%)
Pulmonary Edema		5 (6.7%)	3 (4.9%)	2 (14.3%)

Table 5A *Echocardiographic and Hemodynamic Characteristics by Tumor Location.*

Clinical features (n=79)	P-Value	Total (N=79)	Death (N=9)	Alive (N=70)
Ejection Fraction (Mean ± SD (N))	0.40	58.6 ± 8.6 (N=78)	56.3 ± 10.6 (N=9)	58.8 ± 8.3 (N=69)
Ejection Fraction (Median (min-max))		60.0 (30.0-74.0)	58.0 (45.0-74.0)	60.0 (30.0-73.0)
Aortic stenosis	1,00	3 (3.8%)	0 (0.0%)	3 (4.3%)
Aortic regurgitation	0,15			
I-II		8 (10,2%)	2 (22.2%)	6 (8.6%)
III-IV		1 (1.3%)	0 (0.0%)	1 (1.4%)
Mitral regurgitation	1,00			
I		24 (30.4%)	3 (33.3%)	21 (30.0%)
II		9 (11.4%)	1 (11.1%)	8 (11.4%)
II		3 (3.8%)	0 (0.0%)	3 (4.3%)
IV		1 (1.3%)	0 (0.0%)	1 (1.4%)
Mitral stenosis	1,00	3 (3,8)	0 (0.0%)	3(3,8)
Tricuspid regurgitation	1,00			
I		12 (15.2%)	1 (11.1%)	11 (15.7%)
II		7 (8.9%)	1 (11.1%)	6 (8.6%)
III		1 (1.3%)	0 (0.0%)	1 (1.4%)
IV		1 (1.3%)	0 (0.0%)	1 (1.4%)
Position in the heart	0,25			
Left Atrium		59 (74.7%)	7 (77.8%)	52 (74.3%)
Right Atrium		7 (8.9%)	0 (0.0%)	7 (10.0%)
Ventricle		4 (5.1%)	0 (0.0%)	4 (5.7%)
Valve		8 (10.1%)	1 (11.1%)	7 (10.0%)

Table 5B *Echocardiographic and Hemodynamic Characteristics by Benign Cardiac Tumor Location.*

Clinical features (n=75)	P-Value	Total (N=75)	Myxoma (N=61)	Other Benign Tumors (N=14)
Ejection Fraction (Mean ± SD (N))	0,09	58.7 ± 8.6 (N=74)	58.1 ± 8.5 (N=60)	61.6 ± 9.2 (N=14)
Ejection Fraction (Median (min-max))		60.0 (30.0-74.0)	60.0 (30.0-73.0)	65.0 (38.0-74.0)
Aortic stenosis	0,47	3 (4.0%)	2 (3.3%)	1 (7.1%)
Aortic regurgitation	0,56			
I-II		8 (10,6%)	8 (13.1%)	0 (0.0%)
III-IV		1 (1.3%)	1 (1.6%)	0 (0.0%)
Mitral regurgitation	0,39			
I		22 (29.3%)	17 (27.9%)	5 (35.7%)
II		9 (12.0%)	6 (9.8%)	3 (21.4%)
II		3 (4.0%)	2 (3.3%)	1 (7.1%)
IV		1 (1.3%)	1 (1.6%)	0 (0.0%)
Mitral stenosis	1,00	3 (4,0%)	3 (4,9%)	0 (0.0%)
Tricuspid regurgitation	0,01			
I		11 (14.7%)	7 (11.5%)	4 (28.6%)
II		7 (9.3%)	3 (4.9%)	4 (28.6%)
III		1 (1.3%)	1 (1.6%)	0 (0.0%)
IV		1 (1.3%)	1 (1.6%)	0 (0.0%)
Position in the heart				
Left Atrium	<.0001	58 (77.3%)	57 (93.4%)	1 (7.1%)
Right Atrium	0.31	6 (8.0%)	4 (6.6%)	2 (14.3%)
Ventricle	0.033	2 (2.7%)	0 (0.0%)	2 (14.3%)
Papillary Fibroelastoma	<.0001			
Aortic valve		4 (5.3%)	0 (0.0%)	4 (28.6%)
Mitral Valve		3 (4.0%)	0 (0.0%)	3 (21.4%)
Tricuspid valve		3 (4.0%)	0 (0.0%)	3 (21.4%)

Surgical Approach and Resection

Table 6A and *6B* show the comparison of operative characteristics between alive and dead patients who urderwent cardiac surgery for primary cardiac tumors. Surgical approaches and methods of extracorporeal circulation do not appear to affect survival. In particular, there was no significant difference in cardiopulmonary bypass (CPB) time (p=0,31) and cross-clamp time (p=0,46). As the majority of tumors is represented by mixoma (n=61, 77,21%), left atriotomy (n=49, 80,3%) is the most used intracardiac surgical approach . The majority of tumors into the atrium, mitral valve, and tricuspid valve tumors were resected by a single atrial approach, whereas aortic valve tumors were commonly resected via aortotomy. Ventricular tumors demonstrated the greatest variety of resection techniques; approximately one third were resected by ventriculotomy; however, other techniques such as extracardiac resection, atrial, and aortic approaches were also used. The majority of tumors were completely resected with negative margins. Cardiac reconstruction with prosthetic material was commonly performed after atrial tumor resection. Conversely, ventricular reconstruction with prosthetic material was uncommon. Valve procedures also varied according to tumor location (*Table 6C*).

The incidence of the major postoperative complication was 8.8% (n=7), and included bleeding requiring reoperation, renal insufficiency requiring dialysis, and acute myocardial infarction requiring angiografy and stent implantation. 31.6% (n=25) of patients had an arrhythmias, the most common being atrial fibrillation. Peri-operative (30 day) mortality was equal to 1.3% (n=1). After discharge, one patients with a diagnosis of a malignant tumor underwent adjuvant chemotherapy and radiotherapy.

Table 6A *Comparison of operative characteristics in relation of survival of patients who urderwent cardiac surgery for primary cardiac tumors in the 3 Center.*

Operative Characteristics (n=79)	P-Value	Total (N=79	Death0/(N=9)	Alive (N=70)
CBP time, minutes (Mean ± SD (N))	0,31	70.7 ± 42.3 (N=71)	50.3 ± 35.0 (N=7)	73.0 ± 42.7 (N=64)
CBP time, minutes (Median (min-max))		58.0 (0.0-205.0)	58.0 (0.0-106.0)	57.5 (10.0-205.0)
Cross-clamp Time, minutes (Mean ± SD (N))	0,46	53.4 ± 36.4 (N=71)	38.7 ± 29.5 (N=7)	55.0 ± 36.9 (N=64)
Cross-clamp Time, minutes (min-max)		43.0 (0.0-185.0)	48.0 (0.0-72.0)	42.5 (0.0-185.0)
Incision				
Sternotomy	1	68 (86.1%)	8 (88.9%)	60 (85.7%)
Minitoracotomy		11 (13.9%)	1 (11.1%)	10 (14.3%)
Approch of CBP	0,29			
Central		67 (84.8%)	7 (77.8%)	60 (85.7%)
Peripheral		10 (12.7%)	1 (11.1%)	9 (12.9%)
Beating Heart		1 (1.3%)	1 (1.6%)	0 (0.0%)
Concommitant Procedures	0,66	16 (20.5%)	2 (25.0%)	14 (20.0%)
Septum tumor implantation	0,056	52 (65.8%)	3 (33.3%)	49 (70.0%)
Approach				
Single atriotomy left	0.42	57 (75.0%)	7 (77.8%)	50 (74.6%)
Single atriotomy right		10 (13.2%)	2 (22.2%)	8 (11.9%)
Biatriotomy		9 (11.8%)	0 (0.0%)	9 (13.4%)
ICU stay, days (Mean ± SD (N))	0.97	2.0 ± 2.8 (N=79)	4.0 ± 7.5 (N=9)	1.8 ± 1.3 (N=70)
ICU saty, days (Median (min-max))		2.0 (0.0-24.0)	2.0 (1.0-24.0)	2.0 (0.0-10.0)
Ejection fraction postoperative (Mean ± SD (N))	0.11	59.4 ± 7.3 (N=79)	54.2 ± 11.1 (N=9)	60.1 ± 6.5 (N=70)
Ejection fraction postoperative (Median (min-max))		60.0 (38.0-70.0)	55.0 (38.0-70.0)	60.0 (38.0-70.0)
Hospital stay, days (Mean ± SD (N))	0.21	8.6 ± 3.7 (N=79)	10.7 ± 5.9 (N=9)	8.4 ± 3.3 (N=70)

Hospital stay, days (Median (min-max))		8.0 (4.0-24.0)	8.0 (5.0-24.0)	8.0 (4.0-21.0)
No Cardiac complications	0,42			
		78 (100.0%)	9 (100.0%)	69 (100.0%)
Cerebral complications	0,42	0 (0,00%)	0 (0,00%)	0 (0,00%)
Aortic regurgitation postoperative	0,13			
I		6 (7.6%)	1 (11.1%)	5 (7.1%)
II		2 (2.5%)	1 (11.1%)	1 (1.4%)
Mitral regurgitation Postoperative	0,11			
I		23 (29.1%)	1 (11.1%)	22 (31.4%)
II		1 (1.3%)	0 (0.0%)	1 (1.4%)
III-IV		1 (1.3%)	1 (11.1%)	0 (0.0%)
Tricuspid regurgitation Postoperative	0,04			
I		18 (22.8%)	1 (11.1%)	17 (24.3%)
II		3 (3.8%)	2 (22.2%)	1 (1.4%)
ECG Postoperative	1,00			
0		67 (84.8%)	8 (88.9%)	59 (84.3%)
1		10 (12.7%)	1 (11.1%)	9 (12.9%)
2		2 (2.5%)	0 (0.0%)	2 (2.9%)
Pacemaker implantation	1,00	4 (5.1%)	0 (0.0%)	4 (5.7%)
Discharge	0,005			
Alive		78 (98.7%)	8 (88.9%)	70 (100.0%)

CBP: Cardiopulmonary Bypass; ICU: Intensive Care Unit.

Table 6B *Comparison of operative characteristics between patients affected by myxomas vs patients affected by other benign tumors in the 3 Center.*

Operative Characteristics (n=75)	P-Value	Total (N=75)	Myxoma (N=61)	Other Benign Tumors (N=14)
CBP time, minutes (Mean ± SD (N))	0.41	70.8 ± 41.4 (N=67)	72.1 ± 40.5 (N=54)	65.5 ± 46.0 (N=13)
CBP time, minutes (Median (min-max))		58.0 (10.0-205.0)	58.0 (26.0-205.0)	54.0 (10.0-165.0)
Cross-clamp Time, minutes (Mean ± SD (N))	0.46	53.0 ± 35.2 (N=67)	54.3 ± 34.7 (N=54)	47.9 ± 38.5 (N=13)
Cross-clamp Time, minutes (min-max)		42.0 (0.0-185.0)	43.5 (0.0-185.0)	38.0 (0.0-131.0)
Incision	0,2			
Sternotomy		64 (85.3%)	54 (88.5%)	10 (71.4%)
Minitoracotomy		11 (14.7%)	7 (11.5%)	4 (28.6%)
Approch of CBP	0.14			
Central		64 (85.3%)	54 (88.5%)	10 (71.4%)
Peripheral		10 (13.3%)	6 (9.8%)	4 (28.6%)
Beating Heart		1 (1.3%)	1 (1.6%)	0 (0.0%)
Concommitant Procedures	1.00	15 (20.3%)	12 (20.0%)	3 (21.4%)
Septum tumor implantation	<.0001	51 (68.0%)	49 (80.3%)	2 (14.3%)
Approach				
Single atriotomy left		54 (75.0%)	49 (80.3%)	5 (45.5%)
Single atriotomy right		9 (12.5%)	3 (4.9%)	6 (54.5%)
Biatriotomy		9 (12.5%)	9 (14.8%)	0 (0.0%)
ICU stay, days (Mean ± SD (N))	0.88	2.1 ± 2.8 (N=75)	2.2 ± 3.1 (N=61)	1.7 ± 1.0 (N=14)
ICU saty, days (Median (min-max))		2.0 (0.0-24.0)	2.0 (0.0-24.0)	2.0 (0.0-4.0)
Ejection fraction postoperative (Mean ± SD (N))	0.65	59.6 ± 7.4 (N=75)	59.4 ± 7.6 (N=61)	60.1 ± 6.7 (N=14)
Ejection fraction postoperative (Median (min-max))		60.0 (38.0-70.0)	60.0 (38.0-70.0)	59.5 (50.0-70.0)
Hospital stay, days (Mean ± SD (N))	0.33	8.7 ± 3.8 (N=75)	8.6 ± 4.0 (N=61)	8.9 ± 2.9 (N=14)
Hospital stay, days (Median (min-max))		8.0 (4.0-24.0)	8.0 (4.0-24.0)	8.0 (5.0-16.0)

No Cardiac complications	0.0006	74 (100.0%)	60 (100.0%)	14 (100.0%)
No Cerebral complications	0.0006	75 (100.0%)	61 (100.0%)	14 (100.0%)
Aortic regurgitation postoperative	1.00			
I		6 (8.0%)	5 (8.2%)	1 (7.1%)
II		2 (2.7%)	2 (3.3%)	0 (0.0%)
Mitral regurgitation Postoperative	0.55			
I		21 (28.0%)	19 (31.1%)	2 (14.3%)
II		1 (1.3%)	1 (1.6%)	0 (0.0%)
III-IV		1 (1.3%)	1 (1.6%)	0 (0.0%)
Tricuspid regurgitation Postoperative	0.16			
I		17 (22.7%)	11 (18.0%)	6 (42.9%)
II		3 (4.0%)	3 (4.9%)	0 (0.0%)
ECG Postoperative				
0	0,18	64 (85.3%)	51 (83.6%)	13 (92.9%)
1		9 (12.0%)	9 (14.8%)	0 (0.0%)
2		2 (2.7%)	1 (1.6%)	1 (7.1%)
Pacemaker implantation	0.57	4 (5.3%)	3 (4.9%)	1 (7.1%)
Discharge	1.00			
Alive		74 (98.7%)	60 (98.4%)	14 (100.0%)

CBP: Cardiopulmonary Bypass; ICU: Intensive Care Unit.

Table 6C *Operative procedures*

Operative Data	Number 79 patients
STERNOTOMY vs MINITORACOTOMY	68/11 (6 port-access)
CBP Time, minutes	70.7 ± 42.3
CCA Time, minutes	53.4 ± 36.4
Atrium Access (Left/Right+Left)	49 (62,02%) / 9 (11,39)
Beating Heart	7 (8,86%)
Peripheral Cannulation	11 (13,92%)
Central Cannulation	68 (86,07%)
Reoperation	1 (1,26%)
CABG	7 (8,86%)
Mitral valve repair	3 (3,79%)
Tricuspid valve repair	2 (2,53%)
Cryoablation tumor site	4 (5,06%)

CBP: Cardiopulmonary Bypass; CCA: Aortic Cross-Clamp; CABG: coronary artery bypass graft.

Survival Analysis

The average time of follow-up was 70 months (range 1 to 138 months). It was performed at clinical examination or with a telephone interview. It was performed in 100% of the population. Follow-up features are described in the following tables (*Table 7A, 7B*).

Figure 7A *Comparison of follow-up clinical in relation of survival of patients who underwent cardiac surgery for cardiac tumor excision.*

Follow-up (FU) (N=70/79)	P-Value	Total (N=79	Death0/(N=9)	Alive (N=70)
Aortic regurgitation FU		11 (15.7%)	0 (0.0%)	11 (15.7%)
Mitral regurgitation FU		23 (32,8)	0 (0.0%)	23 (32,8)
Masses recidives FU	1,00	2 (2.5%)	0 (0.0%)	2 (2.9%)
ECG FU				
RS		59 (84.3%)	0 (0.0%)	59 (84.3%)
Atril Fibrillation		6 (8.6%)	0 (0.0%)	6 (8.6%)
PM		5 (7.1%)	0 (0.0%)	5 (7.1%)
New York Heart Association Classification (NYHA class)				
0		27 (38.6%)	0 (0.0%)	27 (38.6%)
I		37 (52.9%)	0 (0.0%)	37 (52.9%)
II		6 (8.6%)	0 (0.0%)	6 (8.6%)
Cardiac complications FU		1 (1.6%)	0 (0.0%)	1 (1.6%)
Ejection fraction FU (Mean ± SD (N)		61.2 ± 6.3 (N=70)		61.2 ± 6.3 (N=70)

FU: Follow-up.

Figure 7B *Comparison of follow-up clinical features between patients affected by myxomas and patients affected by other benign cardiac tumors.*

Follow-up (FU) (N=70/79)	P-Value	Total (N=75)	Myxoma (N=61)	Other Benign Tumors (N=14)
Aortic regurgitation FU	0.44	11 (16.4%)	8 (14.8%)	3 (23.1%)
Mitral regurgitation FU	0.099			
I		21 (31.3%)	19 (35.2%)	2 (15.4%)
II		1 (1.5%)	0 (0.0%)	1 (7.7%)
Masses recidives FU	1.00	1 (1.3%)	1 (1.6%)	0 (0.0%)
ECG FU	0.69			
RS		56 (83.6%)	44 (81.5%)	12 (92.3%)
Atril Fibrillation		6 (9.0%)	6 (11.1%)	0 (0.0%)
PM		5 (7.5%)	4 (7.4%)	1 (7.7%)
New York Heart Association Classification (NYHA class)	0.20			
0		26 (38.8%)	18 (33.3%)	8 (61.5%)
I		35 (52.2%)	30 (55.6%)	5 (38.5%)
II		6 (9.0%)	6 (11.1%)	0 (0.0%)
Cardiac complications FU	0.20	61 (100.0%)	51 (100.0%)	10 (100.0%)
Ejection fraction FU (Mean ± SD (N))	0.63	61.3 ± 6.4 (N=67)	61.4 ± 6.7 (N=54)	61.0 ± 5.5 (N=13)
Ejection fraction FU (Median (min-max)		62.0 (38.0-72.0)	62.5 (38.0-72.0)	62.0 (50.0-70.0)

FU: Follow-up.

The following chart shows the survival curve of the entire population: after surgical resection, long-term survival was satisfactory, equal to 77.64% (*Figure 9*). *Figure 10* shows the survival curve between patients with benign tumors versus patients with malignant tumors. Malignant tumors, showed as expected worse long-term survival than benign ones, due to malignant biology and

incomplete resection. In contrast, benign tumors are not characterized by infiltrative growth and therefore surgery is technically simpler and radical in most cases.

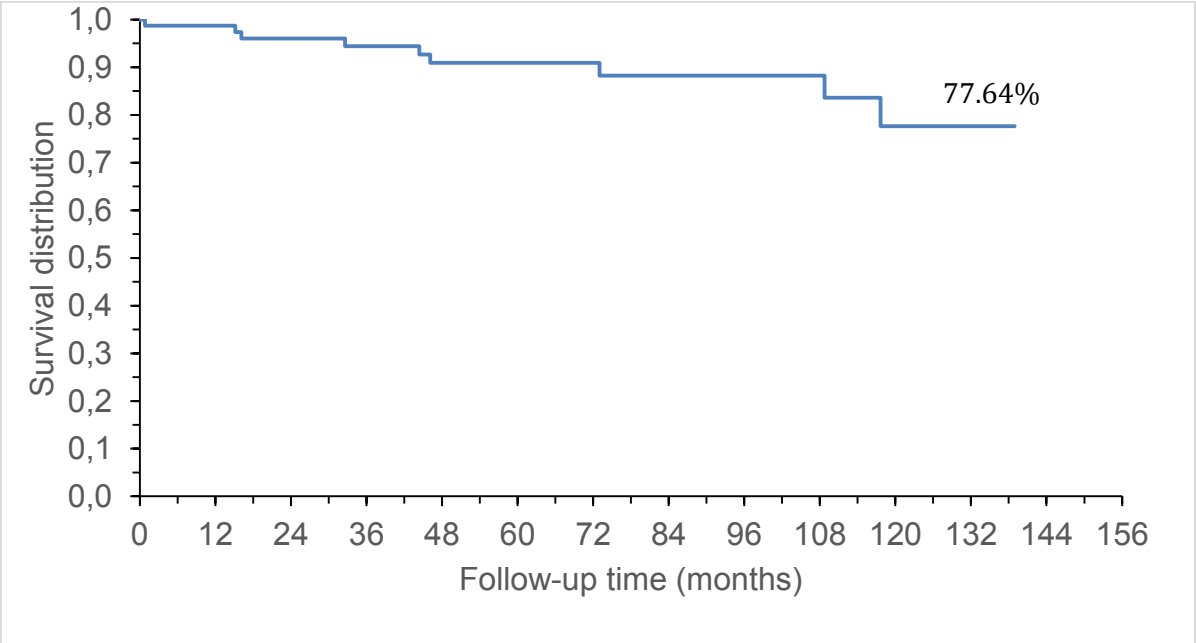


Figure 9 *Survival curve of the entire population after benign and malignant tumors surgical resection.*

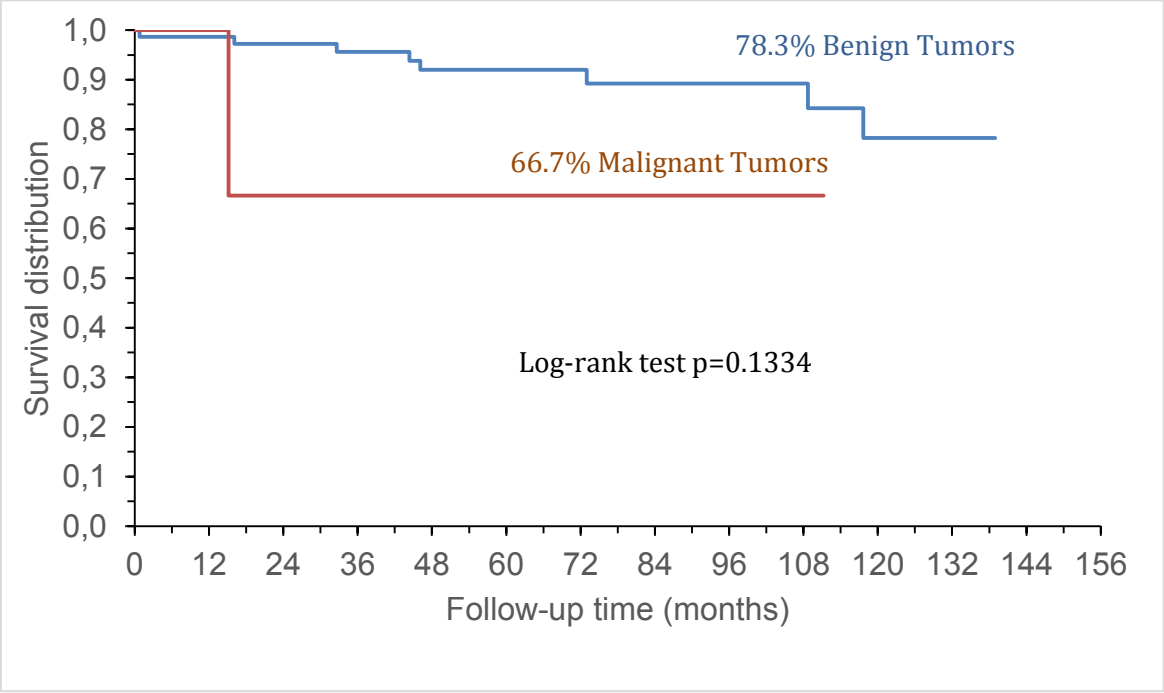


Figure 10 *Survival curve between patients with benign tumors versus patients with malignant tumors after surgical resection.*

Further analysis has been made on the freedom of relapse and therefore of reintervention. In the entire population, only two patients underwent re-intervention for tumor recurrence (1 recurrent myxoma and 1 angiosarcoma).

The deceased patients in the population are 9 (11%). In most cases, death was caused by extra-cardiac malignancies (n=5). There was 1 intra-hospital death due to sepsis. In 3 cases it was not possible to determine the causes of death in the long term.

By comparing clinical variables in relation to survival, Ejection Fraction (FE Basal/FE Postop p=0,3688; FE Basal/FE FU p=0,0067) and NYHA class (p=0,0235) both improved over time with a statistically significant trend (*Table 8A, 8B, Table 9).*

Table 8A, 8B ***A****. Basal Ejection Fraction vs Postoperative Ejection Fraction.* ***B*** *Basal Ejection Fraction vs Follow-up Ejection Fraction. Evaluated by Wilcoxon Test.*

A

Variable	N	Mean	Std Dev	Minimum	Maximum	Median	Lower Quartile	Upper Quartile	p-value Wilcoxon signed rank test
FE	78	58.55	8.57	30.00	74.00	60.00	55.00	65.00	0,3688
FE Postop	78	59.41	7.35	38.00	70.00	60.00	57.00	65.00	
FE Basal	78	-0.86	6.42	-20.00	20.00	0.00	-2.00	0.00	

B

Variable	N	Mean	Std Dev	Minimum	Maximum	Median	Lower Quartile	Upper Quartile	p-value Wilcoxon signed rank test
FE									
FE	69	58.84	8.31	30.00	73.00	60.00	56.00	65.00	0,0067
FU	69	61,13	6,33	38.00	72.00	62.00	60.00	65.00	
FE	69	-2,29	6.83	-22.00	12.00	0.00	-5.00	0.00	
Basal									

Wilcoxon Test is a statistical comparison non parametric that applies in the case of a single sample (FE Ejection Fraction) with two paired measurements. FE: Ejection Fraction; FE Basal: Basal Ejection Fraction; FE Postop: Postoperative Ejection Fraction; FE FU: Follow-up Ejection Fraction.

Table 9 *NYHA Class Basal versus Follow-up (p=0,0235). Evaluated by extension McNemar test (Bowman Test).*

NYHA Class Basal vs NYHA Class FU					
N=70					
Frequency of Classes	0	I+II	III+IV	Total	
0	12 37,50	20 62,50	0 0,00	32	McNemar test extension p=0,0235
I+II	13 43,33	17 56,67	0 0,00	30	
III+IV	2 25.00	6 75,00	0 0,00	8	
Total	27	43	0	70	

(Bowman Test) McNemar test extension was used to determine a statistical relation between identical variables belonging to the same population, before and after an event, such as cardiac surgery. NYHA Class: New York Heart Association; FU: Follow-up.

DISCUSSION AND CONCLUSIONS

Epidemiological data of primary cardiac tumours are still based on post-mortem studies. The incidence and prevalence of cardiac neoplasms, in general, have shown little change over time. Since the early report in 1934 (1-3), the reported prevalence is very low, ranging from 0.0017 to 0.28% in autopsy series, with the variability being strongly influenced by when and where the data have been collected and according to diagnostic methods (4-6). In fact, some years later the era of "surgical pathology" started with the advent of cardiac imaging and open heart surgery, when cardiac neoplasms were diagnosed during life and not only in the autopsy room and became surgically resectable with excellent long-term survival. Cardiac non invasive imaging through transthoracic and transesophageal echocardiography easily detects heart masses. Cardiac magnetic resonance imaging and computed tomography are helpful complementary investigations, for refining diagnosis and in the post-surgery follow-up. Histology with immuno-histochemistry of any cardiac mass is mandatory for diagnosis, therapy and prognosis. For this reason our study is focused on this new perspective: study of epidemiology and surgical pathology of primary cardiac tumors on this new population, because today diagnosis and treatment of surgically resected cardiac tumours have an important and expanding role. Was created a Registry of Veneto Region based on the population of patients subjected to surgical resection for primary cardiac tumor. In Veneto Region, the total number of patients undergoing surgical resection for cardiac tumors within 12 years was 279. According to the Census Data of Veneto Region, the median of resident population was 4.876.601 in the time interval 2005-2016. The annual average incidence in the general population of Veneto Region is 0.47% (from 0,33% to 0,64%). This general data is similar to previus studies. Our results showes that 91,03% of primary cardiac tumors were benign and 8,9% malignant; such distribution corresponds to the results described in the literature (7-18). Approximately 85% of benign tumor were myxomas and 90% of malignant tumors were angiosarcomas and fibrosarcomas. In infants and children, the most dominant cardiac tumor was

rhabdomyoma, which is similar to the population we have observed. There is a peaked age distribution on population having the highest risk of benign cardiac tumor formation between 60 and 70 years old; malignant cardiac tumor having the highest risk at the age og 50-60. Benign cardiac tumors do have a significant propensity for left sided cardiac structures with myxomas sharing their most common origin from left atrial structures (91%) and fibroelastomas having their most common origin at aortic valve leaflets (47,9%) and mitral valve leaflets (27,1%) (19-20). In opposition to, malignant cardiac tumors which have a propensity for the right side of the heart.

In the second phase of our study we have have analyzed the survival rate after the surgical resection. Some of the earliest surgical series have reported patients who underwent cardiac myxoma resection as having an very-good long-term survival characteristics (21), our study document related to these patients showed no difference in terms of survival in the follow-up (21-23). Long-term survival of benign tumors was influenced by preoperative risk factors, ipertension and coronarary artery disease, that was a predictors of mortality. Regarding malignant primary cardiac, those are rare, but their survival after surgical resection was lower due to the infiltrating characteristics of the neoformation and the difficulties of the total resection. For this reason, we had one patient that had multiple recurrences and underwent a reoperation. Also one myxoma had a recurrence. Although, some authors insist on wide resection to prevent recurrence following incoplete resection (24) and some others reports claim that simple tumor resection is sufficient because of the low recurrence rate (1,25), our recurred patients underwent total resection including reconstruction of interatrium defect and atrium side tumor pedicle. Probably the aggresive angiosarcoma in the first case and the multiple locations in the second case have determined reoperations like many reports describing (7, 24,25) patients with multiple recurrences occuring predominately in patients with myxoma.

The clinical presentation of our population was different and dependends of primary cardiac tumors characteristics, similar to the literature series (4). The majority of patients presents dyspnea and

angina, and some patients have other symptoms such as lipothymia, arrhythmia and barkin cough. Systemic embolism was about 8,9 % of patients and most of theme was cerebral embolism. Pulmonary embolism was rare and required emergency operation. About the 24,1 % of patients were asymptomatic.

We identified preoperative, postoperative and follow-up NYHA class and we found improvement of the functional class. Preoperative NYHA functional classification has been implicated as a predictor of survival in many types of cardiac surgery (26). Although not surprising that also we also have an increasing of ejection fraction after tumors resection.

Since the first successful resection of a cardiac tumor was a case of left atrial myxoma, as reported by Crafoord in 1954 (27), cardiac tumors resection gradually bacame a common operation with a very small risks and with a favorable prognosis (28). We performed 68 patients with standard sternotomy and eleven patients with minimally-invasive approach, that become a conventional practice in other cardiac surgery procedures. Reber D et al have demonstrated that the left atrial myxoma resection via median sternotomy as a safe surgery with minimal mortality and minimal rate and recurrence (29) and it has been considered in our experience a routine approach. In some cases of small right side myxoma, small mitral valve and tricuspid valve fibroelastoma and one lipoma of interatrium septum we have performed an anterior minithoracotomy approach that is an exellent route for the right and left atrium. We did not find significant differences beetween the two approach in terms of morbidity and mortality and recurrences. Similar results were noted by Pineda et al, when they evaluated 39 patients (22 with minimally invasive approach and 17 with median sternotomy) who had benign cardiac mass excision. They demonstrated that there were no significant differences in postoperative complications including mortality (30). The mass position must address surgical approach (31). Cardiac tumors arise mainly from the left atrium septum (32) especially on our bigger myxoma population and this position was significant in term of survival also in the myxoma group. Three surgical approaches can be applied: left atriotomy, right atriotomy and biatriotomy. Although the second and the third aprroach have been performed in

many hospital but the true surgical approach is still controversial. In the present study the first choise approach was the left atriotomy. Although some investigators (7,33) prefer the right atriotomy because they didn't observe any recurrences (7,24,25). We consider the side access for almost all right cardiac masses. If the tumors was too big or its stalk was too sessile the complete resection biatriotomy was performed. Any attachment to the tumor was resected widely and sometimes we perfomed associated procedures such as atrial patch closure or right atrium patch reconstruction. Non myxoma cardiac tumors have arisen at various locations and for this reason, it is difficult to establish a regular surgcal strategy (7-16).

Atrial arrhythmia occurred in 31,6 % of patients in our center and it was the most common complication, moreover four patients needed a permanent pacemaker, those results are similar to the one of the large Pineda's series (34).

In conclusion, we have shown a consecutive series of cardiac tumors treated surgically in Veneto Region revealing the prevalence and pathological characteristics. Prognosis of rare cardiac primary tumors is favorable after surgical resection with a minimal morbidity and mortality. The location of the tumor is an important clinical indicator as to the histology of the various primary cardiac tumors. Clinical manifestations of cardiac tumors depend on the type of tumor, location, size, and friability, and can include symptoms related to the valvular or inflow-outflow tract obstruction, arrhythmias, thromboembolism, or constitutional symptoms.

The strongest predictors of mortality are closely linked to the tumor histology, but also include preoperative clinical characteristics. Patients with myxoma has revealed the most most common cardiac tumors and there wasn't significant difference between other benign tumors in terms of survival. Minimally-invasive approach should be considered an option for selected patiens. The complete surgical resection of all of the tumors offers excellent long-term survival for the most patients and minimal recurrence rate.

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